Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Yondelis I.V. infusion 0.25 mg, Yondelis I.V. infusion 1 mg
[Non-proprietary name]	Trabectedin (JAN*)
[Applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	January 5, 2015

[Results of deliberation]
In the meeting held on August 31, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. The drug substance and the drug product are both classified as poisonous drugs, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data for the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as soon as possible, and taking necessary measures to ensure its proper use.

**Japanese Accepted Name (modified INN)*

Review Report

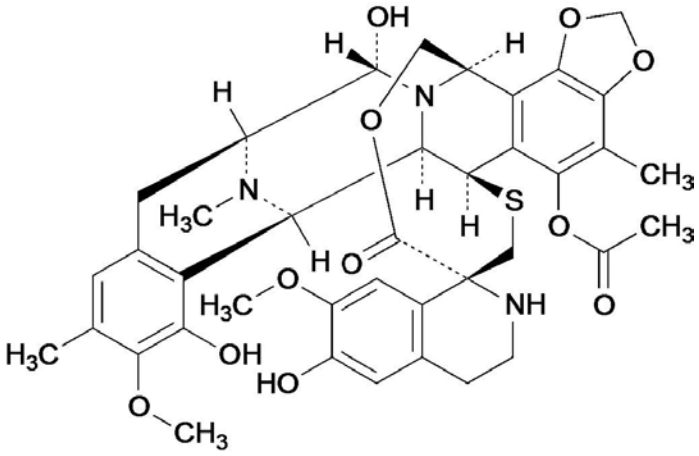
August 20, 2015
Pharmaceuticals and Medical Devices Agency

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]	Yondelis I.V. infusion 0.25 mg, Yondelis I.V. infusion 1 mg
[Non-proprietary name]	Trabectedin
[Applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	January 5, 2015
[Dosage form/Strength]	Lyophilized powder for solution for infusion: Each vial contains 0.25 mg of Trabectedin Lyophilized powder for solution for infusion: Each vial contains 1 mg of Trabectedin

[Application classification] Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{39}H_{43}N_3O_{11}S$

Molecular weight: 761.84

Chemical name: (1'*R*,6*R*,6a*R*,7*R*,13*S*,14*S*,16*R*)-6',8,14-Trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-19-oxo-3',4',6a,7,12,13,14,16-octahydro-2'*H*,6*H*-spiro[6,16-(epithiopropanooxymethano)-7,13-epiminobenzo[4,5]azocino[1,2-*b*][1,3]dioxolo[4,5-*h*]isoquinolin-20,1'-isoquinolin]-5-yl acetate

[Items warranting special mention]

Orphan drug (Drug Designation No. 245 of 2011 [*23 yaku*]; PFSB/ELD Notification No. 0610-1 dated June 10, 2011, by the Director of 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

August 20, 2015

[Brand name]	Yondelis I.V. infusion 0.25 mg, Yondelis I.V. infusion 1 mg
[Non-proprietary name]	Trabectedin
[Applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	January 5, 2015

[Results of review]

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the submitted data demonstrate that trabectedin has a certain degree of efficacy in treating soft tissue sarcomas and its safety is acceptable in view of its observed benefits. However, hepatic failure/hepatic impairment, myelosuppression/febrile neutropenia, and rhabdomyolysis as adverse events need to be investigated through post-marketing surveillance.

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

[Indication]

Soft tissue sarcomas

[Dosage and administration]

The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition.

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data for the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as soon as possible, and taking necessary measures to ensure its proper use.

Review Report (1)

July 14, 2015

I. Product Submitted for Registration

[Brand name]	Yondelis I.V. infusion 0.25 mg, Yondelis I.V. infusion 1 mg
[Non-proprietary name]	Trabectedin
[Applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	January 5, 2015
[Dosage form/Strength]	Lyophilized powder for solution for infusion: Each vial contains 0.25 mg of Trabectedin Lyophilized powder for solution for infusion: Each vial contains 1 mg of Trabectedin
[Proposed indications]	Soft tissue sarcomas of the following histological subtypes: myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, alveolar soft part sarcoma, clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, giant cell fibroblastoma, and endometrial stromal sarcoma.

[Proposed dosage and administration]

The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition.

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

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

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

1.(1) Summary of the proposed drug product

Trabectedin, developed by PharmaMar, S.A. in Spain, is a compound with a tetrahydroisoquinoline skeleton and was originally isolated from a sea squirt *Ecteinascidia turbinata*. Trabectedin is assumed to bind to the minor groove of deoxyribonucleic acid (DNA), inducing cell death and cell cycle arrest

through mechanisms including inhibition of the nucleotide excision repair pathway, thereby suppressing tumor growth.

1.(2) History of development

Outside Japan, PharmaMar, S.A. started a phase I study in patients with solid cancer (Study ET-A-002-95) in May 1996, and a phase II study in patients previously treated with chemotherapy for unresectable liposarcoma or leiomyosarcoma (Study ET-743-STS-201) in May 2003. In the European Union (EU), PharmaMar filed a new drug application mainly based on the results of Study ET-743-STS-201 in July 2006, obtaining approval for trabectedin in September 2007 for the following indication: "Yondelis is indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents." At the time of the approval, the European Medicines Agency (EMA) instructed PharmaMar to identify the patient population that would benefit most from trabectedin. PharmaMar thus started a phase III study in November 2008 in chemotherapy-naïve patients with unresectable soft tissue sarcoma (STS) of histological subtypes reported to carry chromosomal translocations (Study ET-C-002-07). However, Study ET-C-002-07 was terminated because an interim analysis conducted in August 2012 predicted that a large number of patients would be required in the second stage. In the United States, Johnson & Johnson Pharmaceutical Research and Development, LLC (currently Janssen Research and Development LLC) started a phase III study in patients previously treated with chemotherapy for unresectable liposarcoma or leiomyosarcoma (Study ET743-SAR-3007) in May 2011. In November 2014, Janssen submitted a new drug application for the treatment of STS mainly based on this study. The application is currently under review.

As of May 2015, trabectedin has been approved in 77 countries/regions for the treatment of STS.

In Japan, the applicant conducted a phase II study in patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations (Study 10045030). The applicant has filed a new drug application mainly based on Study 10045030.

In June 2011, trabectedin was designated as an orphan drug for the intended indication of "soft tissue sarcomas with chromosomal translocations" (Drug Designation No. 245 of 2011[*23 yaku*]).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

[redacted]

2.A.(1).1) Characterization

The drug substance is a white powder, and its description, melting point, solubility, hygroscopicity, pH, dissociation constant, distribution coefficient, and optical rotation have been studied.

The chemical structure of the drug substance was confirmed by elemental analysis, infrared absorption spectroscopy (IR), nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectroscopy, ultraviolet and visible absorption spectroscopy (UV/Vis), mass spectrometry, and single-crystal X-ray structural analysis.

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

See the attachment.

2.A.(1).3) Control of drug substance

[redacted]

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

The stability study of the drug substance is summarized in the table below. Photostability testing showed that the drug substance was photostable.

Stability study of the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	- 20 ± 5°C	–	[redacted]	[redacted] months

[redacted]

2.A.(2) Drug product

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

The drug product is a lyophilized powder for solution for infusion. Each vial contains 0.25 mg or 1 mg of trabectedin. The drug product contains sucrose, potassium dihydrogen phosphate, phosphoric acid, and potassium hydroxide as excipients.

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

[redacted]

2.A.(2).3) Control of drug product

The proposed specifications of the drug product include content, description, identification (UV/Vis), pH, purity (appearance of solution and related substance [HPLC]), water content, bacterial endotoxins, uniformity of content (mass variation), foreign insoluble matter, insoluble particulate matter, sterility, and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability study of the drug product is summarized in the table below. Photostability testing showed that the drug product was photostable.

Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	5 ± 3°C	–	Glass vial with a rubber stopper covered with a flip-off cap	60 months
Accelerated	3 production batches	25 ± 2°C	60 ± 5% RH		6 months

Based on the above results, a shelf-life of 60 months has been proposed for the drug product when stored in glass vial, sealed with a butyl rubber stopper covered with a polypropylene/aluminum flip-off cap at 5 ± 3°C.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product was adequately controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Pharmacological characteristics

Trabectedin is known to bind to the minor groove of DNA (*Biochemistry.* 1996;35:13303-9), thereby exhibiting pharmacological actions shown below:

Trabectedin has been reported to:

- Induce cell death and cell cycle arrest (*Cell Prolif.* 2007;40:885-904) by inhibiting the transcription-coupled pathway of nucleotide excision repair (e.g., *Nat Med.* 2001;7:961-6).
- Regulate transcription of the gene clusters involved in cell proliferation (e.g., *Proc Natl Acad Sci USA.* 2000;97:6775-9), inhibit cytokine production (*Cancer Res.* 2005;65:2964-71), and induce apoptosis of mononuclear phagocytes including tumor-associated macrophages (*Cancer Res*. 2010;70:2235-44; *Cancer Cell*. 2013;23:249-62), and exert other effects.

- Inhibit the function of FUS-CHOP and EWS-FL11 proteins (transcription factors) by inhibiting their binding to DNA, thereby suppressing the expression of cancer-related genes such as CHOP and NR0B1 (*Mol Cancer Ther.* 2009;8:449-57; *Neoplasia*. 2011;13:145-53). FUS-CHOP and EWS-FL11 proteins are known to be expressed in human soft tissue sarcomas (STS) with chromosomal translocations.
- Induce the differentiation of human myxoid liposarcoma tissue into normal adipose tissue by increasing the expression of transcription factors involved in adipocyte differentiation (e.g., *Mol Cancer Ther.* 2009;8:449-57).

3.(i).A.(1).2) Effects on STS cell lines

i) *In vitro* study (Report 13SA01)

The antiproliferative effects of trabectedin against 16 human STS cell lines were investigated. The results, expressed as IC_{50}, are shown in the table below. The geometric mean IC_{50} was 0.325 nmol/L for cell lines with chromosomal translocations (7 cell lines) and 0.837 nmol/L for cell lines without chromosomal translocations (9 cell lines). The geometric mean ratio of IC_{50} [95% confidence interval (CI)] (with translocations/without translocations) was 0.388 [0.172, 0.875].

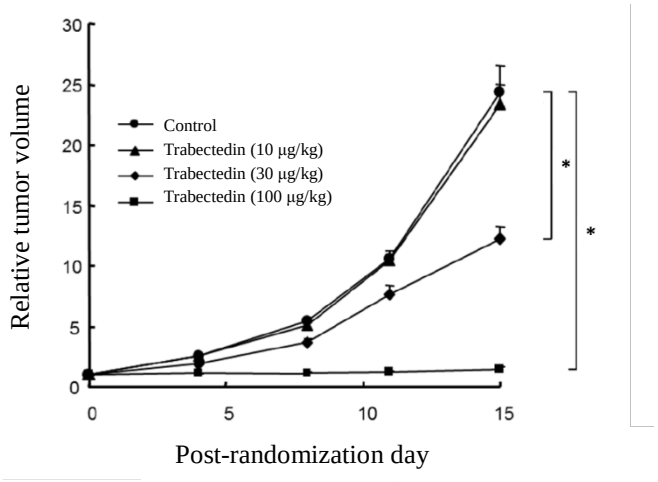
Antiproliferative effects of trabectedin against human STS cell lines

Chromosomal translocation	Cell line	Histological subtype	IC_{50} (nmol/L) [95% CI]
Positive	SYO-1	Synovial sarcoma	0.145 [0.131, 0.160]
	SK-ES-1	Ewing's sarcoma	0.196 [0.179, 0.214]
	RD-ES	Ewing's sarcoma	0.257 [0.184, 0.357]
	Aska-SS	Synovial sarcoma	0.298 [0.259, 0.343]
	Yamato-SS	Synovial sarcoma	0.403 [0.363, 0.448]
	SCCH-196	Small round cell tumor	0.642 [0.546, 0.754]
	SJCRH30	Alveolar rhabdomyosarcoma	0.683 [0.622, 0.750]
Negative	KYM-1	Rhabdomyosarcoma	0.205 [0.195, 0.217]
	SW872	Liposarcoma	0.380 [0.306, 0.471]
	Hs925.T	Pagetoid sarcoma	0.457 [0.425, 0.491]
	SW982	Synovial sarcoma	0.608 [0.497, 0.745]
	RD	Rhabdomyosarcoma	0.867 [0.810, 0.927]
	SK-LMS-1	Leiomyosarcoma	1.165 [1.070, 1.269]
	HT-1080	Fibrosarcoma	1.688 [1.589, 1.794]
	RKN	Leiomyosarcoma	1.929 [1.776, 2.094]
	SKN	Leiomyosarcoma	2.846 [2.223, 3.644]

n = 6

ii) *In vivo* studies (Reports 13TA01, 13TA02, 13TA03, 13TA04, 13TA05, and 13TA06)

The antiproliferative effects of trabectedin against tumor cells were investigated using athymic nude mice inoculated subcutaneously with human synovial sarcoma cell lines SYO-1. The nude mice were randomized on post-inoculation day 9 (tumor volume of 100 to 300 mm^3). The mice received intravenous doses of 10, 30, or 100 μg/kg of trabectedin on post-randomization days 1, 5, and 9. Tumor volume was calculated on post-randomization day 15. Compared with the control (phosphate buffer), trabectedin 30 and 100 μg/kg showed statistically significant antiproliferative effects against tumor cells ($p < 0.01$, Williams' test), as shown in the diagram below.



Antiproliferative effects of trabectedin against tumor cells

n = 8
mean ± standard deviation (SD) (Only mean + SD is shown in the diagram.)
* p <0.01 compared to the control group
Relative tumor volume = (tumor volume on day n post-randomization)/(tumor volume on the randomization day)

The antiproliferative effects of trabectedin against tumor cells were investigated using athymic nude mice inoculated subcutaneously with cell lines with chromosomal translocations, SK-ES-1 and SJCRH30, or cell lines without chromosomal translocations, KHOS/NP, RD and SK-LMS-1. The nude mice were randomized on post-inoculation day 6 or 10 (tumor volume of 100 to 300 mm^3). The mice received an intravenous dose of 100 μg/kg of trabectedin on post-randomization days 1, 5, and 9. Tumor volume was calculated on post-randomization day 15. Compared with the control (phosphate buffer), trabectedin showed statistically significant antiproliferative effects against tumor cells (p <0.01, Welch's t-test) in all cell lines (see the table below).

Antiproliferative effects of trabectedin against tumor cells

Chromosomal translocation	Cell line (Histological subtype)	Group	Relative tumor volume*1 (Mean ± SD)	Tumor growth inhibition*2 (%)
Positive	SK-ES-1 (Ewing's sarcoma)	Control	13.69 ± 0.67	62.7
		Trabectedin	5.11 ± 0.17	
	SJCRH30 (Alveolar rhabdomyosarcoma)	Control	15.23 ± 0.67	48.8
		Trabectedin	7.80 ± 0.56	
Negative	KHOS/NP (Osteosarcoma)	Control	19.85 ± 0.58	73.6
		Trabectedin	5.24 ± 0.56	
	RD (Rhabdomyosarcoma)	Control	9.52 ± 0.44	56.0
		Trabectedin	4.19 ± 0.26	
	SK-LMS-1 (Leiomyosarcoma)	Control	32.58 ± 2.86	38.4
		Trabectedin	20.06 ± 1.46	

n = 8
*1, Relative tumor volume = (tumor volume on post-randomization day 15) / (tumor volume on the randomization day)
*2, Tumor growth inhibition = [(relative tumor volume in the control group) - (relative tumor volume in the trabectedin group)] / (relative tumor volume in the control group) × 100

3.(i).A.(2) Secondary pharmacodynamics (Reference data, *Eur J Cancer*. 2002;38:1395-404)

The antiproliferative effects of trabectedin against haematopoietic progenitors was studied by colony formation assay using human bone marrow cells. The IC_{50} (mean ± standard error) of trabectedin (after 24-hour treatment) was 50 ± 10 nmol/L in colony forming unit-granulocyte/macrophage (CFU-GM),

30 ± 5 nmol/L in burst-forming unit-erythroid (BFU-E), 10 ± 1 nmol/L in colony forming unit-megakaryocyte (CFU-Meg), and 40 ± 15 nmol/L in multilineage progenitor cells (CFU-Mix).

Since CFU-Meg progenitors were more sensitive to trabectedin than other haematopoietic progenitors, thrombocytopenia may occur following administration of trabectedin. The applicant plans to provide a cautionary statement regarding the risk of thrombocytopenia in the package insert.

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

3.(i).A.(3).1) Effects on the central nervous system (Report [redacted])

A single intravenous dose of 12.5, 25, or 50 μg/kg of trabectedin was administered to rats (5 males/group) to investigate the effects on clinical signs and behavior. No significant effects of trabectedin were observed.

3.(i).A.(3).2) Effects on the cardiovascular and respiratory systems

i) Effects on human ether-a-go-go-related gene potassium channels (Reference data, Report [redacted] [non-GLP study])

The effects of trabectedin on the human ether-a-go-go-related gene (hERG) potassium channel were investigated using hERG-transfected human embryonic kidney 293 (HEK293) cell lines. Trabectedin 0.01 to 3 μmol/L showed no effects, but trabectedin 10 μmol/L inhibited approximately 10% of hERG potassium channels.

ii) Effects on blood pressure, electrocardiograms, and other parameters (Report [redacted])

A dose of 90 μg/kg of trabectedin was administered by intravenous infusion to anaesthetized cynomolgus monkeys (4 males/group) over 1 hour to study the effects on heart rate, electrocardiograms (ECGs; e.g., PR interval and QT interval), cardiac output, stroke volume, arterial blood pressure (mean, systolic, and diastolic), and respiratory function. The results showed that there was a decrease in arterial blood pressure (mean, systolic, and diastolic) following administration of trabectedin.

Given that blood pressure decreases in anaesthetized animals (e.g., *J Auton Pharmacol.* 1986;6:9-14), the observed decrease in blood pressure may be attributable to anaesthesia, and whether a causal relationship exists between the arterial blood pressure and trabectedin is difficult to determine. However, in addition to the above results, trabectedin-induced low blood pressure has been reported in foreign post-marketing surveillance. Therefore, the applicant plans to include a cautionary statement regarding low blood pressure in the package insert.

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

Based on the submitted data and following discussion, PMDA concluded that trabectedin can be expected to be effective in the treatment of STS.

Mechanism of action and efficacy of trabectedin

The applicant's explanation on the mechanism of action and the efficacy of trabectedin in the treatment of STS:
Trabectedin is assumed to bind to the DNA minor groove, inducing cell death and cell cycle arrest through mechanisms including inhibition of the nucleotide excision repair pathway, thereby suppressing tumor growth [see "3.(i).A.(1).1) Pharmacological characteristics"].

In addition to the above mechanism of action, trabectedin has been shown by non-clinical studies to suppress the growth of human STS cell lines of several histological subtypes with and without chromosomal translocations [see "3.(i).A.(1).2) Effects on STS cell lines"]. Therefore, trabectedin is expected to be effective against various histological subtypes of STS.

Furthermore, trabectedin has been reported to inhibit the transcriptional function of fusion proteins resulting from chromosomal translocations, thereby suppressing the expression of cancer-related genes [see "3.(i).A.(1).1) Pharmacological characteristics"], and has been shown by an *in vitro* study to have higher antiproliferative effects against cell lines with chromosomal translocations than against those without chromosomal translocations [see "3.(i).A.(1).2).i) *In vitro* study"]. These findings suggest that trabectedin may be more effective against STS with chromosomal translocations than against STS without chromosomal translocations.

PMDA's view:
The applicant's explanation is generally acceptable. However, given that the relationship between chromosomal translocations and the efficacy of trabectedin may be an important factor in predicting clinical efficacy and for selecting patients, the applicant should continue to collect relevant information and inform healthcare professionals of any new findings in an appropriate manner.

3.(ii) Summary of pharmacokinetic studies

[redacted] The pharmacokinetics (PK) of trabectedin in animals was studied in mice, rats, and monkeys. Human or animal biological samples were used for the analyses of plasma protein binding, drug metabolizing enzymes, transporters, and other parameters of trabectedin.

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

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

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

A single dose of 200 μg/kg of trabectedin was administered intravenously as a bolus injection to male and female mice, to evaluate plasma trabectedin concentrations (see table below). There were no obvious differences in PK parameters of trabectedin between sexes. The clearance (CL) and the volume of distribution (V_z) of trabectedin were approximately 1/3 of the rate of mouse hepatic blood flow (approximately 5.2 to 5.4 L/h/kg), and approximately 30-fold the mouse body fluid volume

(approximately 0.6 L/kg), respectively (*Pharm Res.* 1993;10:1093-5; *J Pharmacokinet Biopharm.* 1980;8:165-76; *Am J Clin Nutr.* 1979;32:630-47; *Am J Physiol Renal Physiol.* 2010;299:F280-3). The applicant explained that trabectedin was considered to be widely distributed in tissues and plasma of mice, taking the level of V_z into consideration.

PK parameters of trabectedin (male and female mice, single-dose intravenous bolus injection)

Sex	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	V_z (L/kg)
Male	92.3	21.1	2.2	20.9
Female	140.2	20.3	1.5	13.4

Since blood samples were collected from different animals at each measuring time point, the PK parameters were calculated based on the mean plasma concentration for each measuring time point (n = 3/measuring time point)

A single dose of 50 μg/kg of trabectedin was administered intravenously either as a 3- or 24-hour infusion to male and female rats, to evaluate plasma trabectedin concentrations (see table below). The AUC_{0-t} was similar in the 3- and 24-hour infusion groups. There were no obvious differences in PK parameters between sexes.

PK parameters of trabectedin (male and female rats, single-dose intravenous infusion)

Duration of infusion (h)	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)
3	M	0.8	0.6	1.7
	F	1.0	0.5	2.9
24	M	0.1	23.2	2.8
	F	0.2	22.9	3.7

Since blood samples were collected from different animals at each measuring time point, the PK parameters were calculated based on the mean plasma concentration for each measuring time point (n = 2/measuring time point)

A single dose of 50 μg/kg of [redacted] or [redacted] of trabectedin was administered to male and female rats over 3 hours intravenously, and the concentrations in plasma were studied (see table below). The C_{max} and AUC_{0-t} were similar in the [redacted] and [redacted]. There were no obvious differences in PK parameters of trabectedin between sexes.

PK parameters of trabectedin (male and female rats, single-dose intravenous infusion)

Test substance	Sex	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	$V_{d,ss}$ (L/kg)
[redacted]	M	1.4	2.4	2.8	4.4	17.7	35.9
	F	0.9	1.9	–	–	–	–
[redacted]	M	1.1	2.4	2.7	2.8	18.6	20.4
	F	1.1	2.2	–	–	–	–

Since blood samples were collected from different animals at each time point, the PK parameters were calculated based on the mean plasma concentration for each measuring time point (n = 2/ measuring time point); –, not calculated

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

Three doses of trabectedin, ranging from 2.5 to 75 μg/kg, were administered to male and female rats as a 3-hour infusion every 3 weeks, to evaluate plasma trabectedin concentrations following the first and the third doses (see table below). There were no obvious differences in PK parameters of trabectedin between sexes at any dose levels or according to the number of doses received. No significant accumulation of trabectedin associated with repeated administration was observed.

PK parameters of trabectedin (male and female rats, repeat-dose intravenous infusion)

Number of doses	Sex	Dose level (μg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)
First	M	10	0.9	3.2	0.9
		25	0.8	2.7	2.2
		50	1.6	0.7	4.8
		75	2.0	2.7	6.0
	F	2.5	0.2	3.2	–
		10	0.5	3.0	0.6
		25	0.5	2.5	1.2
		50	1.3	2.5	3.3
Third	M	10	0.4	2.7	0.6
		25	1.3	3.2	2.2
		50	1.9	0.7	7.4
	F	10	0.3	2.6	0.7
		25	1.0	3.1	2.2
		50	1.3	3.1	8.6

Since blood samples were collected from different animals at each measuring time point, the PK parameters were calculated based on the mean plasma concentration for each measuring time point (n = 2/ measuring time point); –, not calculated.

Male and female monkeys received trabectedin as a 3- or 24-hour infusion according to the schedules shown below. Plasma trabectedin concentrations were evaluated (see table below): (a) after 3 doses of 25, 50, or 75 μg/kg of trabectedin were administered as a 3-hour intravenous infusion every 3 weeks, a dose of 120, 75, or 100 μg/kg of trabectedin, respectively, was administered as the fourth dose, as a 3-hour intravenous infusion; or (b) after 3 doses of 75 μg/kg of trabectedin were administered as a 24-hour infusion every 3 weeks, a dose of 100 μg/kg of trabectedin was administered as the fourth dose, as a 24-hour intravenous infusion. There were no obvious differences in PK parameters of trabectedin between sexes at any dose levels or according to number of doses received. The CL and the steady-state volume of distribution ($V_{d,ss}$) of trabectedin were approximately one half the rate of monkey hepatic blood flow (approximately 2.6 to 3.1 L/h/kg), and approximately 120- to 780-fold the monkey body fluid volume

(approximately 0.7 L/kg), respectively (*Pharm Res.* 1993;10:1093-5; *J Pharmacokinet Biopharm*. 1980;8:165-76; *Am J Clin Nutr.* 1979;32:630-47). The applicant explained that trabectedin was considered to be widely distributed in tissues and plasma of the monkey, taking the level of $V_{d,ss}$ into consideration.

PK parameters of trabectedin (male and female monkeys, repeat-dose intravenous infusion)

Duration of infusion (h)	Number of doses	Sex	Dose level (μg/kg)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	$V_{d,ss}$ (L/kg)
3	First	M	25	0.8	7.79	41	3.2	142
			50	2.8	22.7	77	2.2	161
			75	3.2	30.3	74	2.5	176
		F	25	0.8	10.9	81	2.3	197
			50	6.8	28.2	77	1.8	80.7
			75	2.6	26.9	96	2.8	287
	Third	M	25	0.8	6.80[*3]	48	3.7	193
			50	5.3	–	173	–	–
			75	1.7	24.3	63	3.1	230
		F	25	1.0	11.3	83	2.2	200
			50	2.9	–	229	–	–
			75	1.4	27.1[*3]	231	2.8	534
	Fourth[*1]	M	75	3.7	34.9	92	2.2	212
			100	–	–	62	–	–
			120	4.3	–	–	–	–
		F	75	5.1	33.5	99	2.2	171
			100	5.6	–	–	–	–
			120	5.7	84.0	137	1.4	219
24	First	M	75	1.8	51.6	109	1.5	106
		F	75	1.0	–	–	–	–
	Third	M	75	1.8	–	–	–	–
		F	75	1.7	–	–	–	–
	Fourth[*2]	M	100	0.8	30.5	81	3.3	292
		F	100	1.2	49.7	74	2.0	167

Since blood samples were collected from different animals at each measuring time point, the PK parameters were calculated based on the plasma concentration for each measuring time point (n = 1/measuring time point).
–, not calculated
*1, From the first to the third dose, 25, 50, or 75 μg/kg of trabectedin was administered as a 3-hour intravenous infusion every 3 weeks, and the fourth dose for each group was increased to 120, 75, or 100 μg/kg, respectively.
*2, From the first to the third dose, the 3 doses of 75 μg/kg of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks;
*3, Values that were estimated based on AUC_{0-t}.

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

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

Tissue distribution of radioactivity was evaluated in male albino rats receiving a single dose of 61 μg/kg of ^{14}C-labelled trabectedin as a bolus intravenous infusion. Radioactivity was distributed in a wide range of tissues. In the majority of tissues, the maximum radioactivity levels were observed 7 minutes after administration, while in the thymus, pituitary, and lymph nodes, the maximum radioactivity levels were observed 48 hours after administration. The radioactivity AUC_{0-24h} was higher compared to that of plasma (10.8 Eq.·h/mL) in the following tissues: the spleen, thyroid gland, lungs, adrenal glands, and lymph nodes (tissue/plasma radioactivity AUC_{0-24h} ratios were 656, 598, 494, 416, and 358, respectively

for the above tissues). In contrast, the radioactivity $AUC_{0\text{-}24h}$ was lower in the eyeball, perirenal adipose tissue, testicles, and brain (31.8, 27.8, 4.4, and 0.2,* respectively) compared with that of other tissues. The radioactivity levels in plasma 24 hours after administration decreased to approximately 3% of the radioactivity levels in plasma measured immediately after administration. At 96 hours after administration, the radioactivity in the thymus was 85% of the maximum level, and the radioactivity detected in the rest of the tissues were 10% to 64% of their maximum levels.

* Tissue/plasma radioactivity $AUC_{0\text{-}24h}$ ratio, measured 7 minutes after administration

Human breast cancer cell line MCF7 was implanted subcutaneously into female nude mice. The grown tumors were transplanted into the mammary glands of female nude mice, which were then given a single dose of 200 μg/kg of ^{14}C-labelled trabectedin as a bolus intravenous injection. The distribution of radioactivity in plasma, and tissues of the mammary gland, the tumors transplanted to the mammary gland, the liver, muscles, and the femur was studied. The maximum radioactivity levels were observed 1 hour after administration in all tissues studied. $AUC_{0\text{-}96h}$ of plasma radioactivity was 143 ng Eq.·h/mL. The tissue/plasma ratio of radioactivity $AUC_{0\text{-}96h}$ was highest in the liver (52), followed by the mammary gland (29), tumors transplanted into the mammary gland (24), the femur (15), and muscles (7).

A single dose of 150 μg/kg of ^{14}C-labelled trabectedin was administered intravenously as a bolus injection to male wild-type albino mice and male albino mdr1a/1b (-/-) mice (which lacked mdr1a and mdr1b genes) to investigate the effects of P-glycoprotein (P-gp) on the tissue distribution of radioactivity. In mdr1a/1b (-/-) mice, the tissue/plasma ratio of radioactivity $AUC_{0\text{-}96h}$ was 5.9 in the brain and 4.0 in the testicles. In wild-type mice, the tissue/plasma ratio of radioactivity $AUC_{0\text{-}96h}$ was 0.51 in the brain and 2.2 in the testicles. Thus, the tissue/plasma ratio of radioactivity $AUC_{0\text{-}96h}$ in mdr1a/1b (-/-) mice was approximately 11.6-fold (the brain) and approximately 1.8-fold (the testicles) those in wild-type mice. According to the applicant, this suggests that P-gp is involved in the tissue distribution of trabectedin and its metabolites.

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

Plasma protein binding of trabectedin was studied by the equilibrium dialysis method. Trabectedin 130 nmol/L was incubated with male/female mouse plasma, male/female rat plasma, female rabbit plasma, male dog plasma, and male monkey plasma at 37°C for 4 hours. Trabectedin 13 and 130 nmol/L was incubated with male human plasma at 37°C for 4 hours. The results showed that the plasma binding of trabectedin was 98.9% and 98.8% in male and female mouse plasma, respectively, 95.3% and 94.9% in male and female rat plasma, respectively, and 90.0%, 99.0%, and 94.4% in female rabbit, male dog, and male monkey plasma, respectively. The binding of trabectedin to male human plasma protein was 97.8% and 97.3% at 13 and 130 nmol/L, respectively, showing that the plasma binding was not concentration-dependent. Binding of trabectedin (13 nmol/L) to human serum albumin and α1-acid glycoprotein (both at physiological concentrations) was studied (*Molecular Pharmacokinetics, 1st ed*. Nanzando, 2008). Protein binding of trabectedin 13 nmol/L was 86.0% for human serum albumin at 43 g/L, and 90.1% and 96.7% for α1-acid glycoprotein at 500 and 1000 mg/L, respectively.

Plasma protein binding of trabectedin was studied by the ultrafiltration method after human plasma was incubated for 1 hour at 37°C with trabectedin (4 nmol/L) and sodium valproate (7 to 700 μmol/L), ceftazidime hydrate (10 to 1000 μmol/L), cloxacillin sodium hydrate (2.5 to 250 μmol/L), diazepam (10 to 1000 nmol/L), erythromycin (1.5 to 150 μmol/L), warfarin potassium (0.25 to 25 μmol/L), tamoxifen (10 to 1000 nmol/L), digitoxin (1 to 100 nmol/L), ondansetron hydrochloride hydrate (10 to 1000 nmol/L), paracetamol (10 to 1000 μmol/L), diclofenac sodium (0.1 to 10 μmol/L), acetylsalicylic acid (10 to 1000 μmol/L), propranolol hydrochloride (50 to 5000 nmol/L), or phenytoin sodium (phenytoin) (4 to 400 μmol/L). After incubation with trabectedin alone, the plasma protein binding of trabectedin was 94.4%, which decreased to 92.9% after incubation with trabectedin and phenytoin (400 μmol/L). In contrast, other agents did not affect the protein binding of trabectedin (with no difference between "incubation with trabectedin alone" and "incubation with trabectedin plus an agent other than phenytoin").

Since humans trabectedin is eliminated mainly by hepatic metabolism [see "4.(ii).A.(2).3) Foreign phase I study"], any change in the protein binding of trabectedin would not affect the concentration of free forms of trabectedin in blood in clinical use. Based on this, the applicant stated that trabectedin and phenytoin were unlikely to cause pharmacokinetic drug interactions involving protein binding.

The distribution of trabectedin in blood cells was studied after 130 nmol/L of trabectedin was incubated with male/female mouse, male/female rat, female rabbit, male dog, or male human whole blood at 37°C for 30 minutes. The results showed that blood to plasma concentration ratios were 0.73 and 0.69 in male and female mice, respectively, 1.51 and 1.46 in male and female rats, respectively, 1.5, 0.69, and 0.89, in female rabbits, male dogs, and male humans, respectively. The applicant explained that based on the results trabectedin appeared to be partially distributed to blood cells.

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

A single dose of 61 μg/kg of ^{14}C-labelled trabectedin was administered to female rats on gestation day 18 by intravenous bolus injection, to investigate the radioactivity distribution in maternal animals and fetuses. While radioactivity was not detected in maternal animal blood measured 8 or 24 hours after administration, radioactivity levels in the fetus were 2.4 and 2.5 ng Eq./mL, respectively. In fetal tissues, radioactivity was not detected in blood, the brain, heart, or kidney at 8 or 24 hours after administration. In the fetal lung, radioactivity levels were 3.8 and 3.2 ng Eq./mL at 8 and 24 hours after administration, respectively. In the fetal liver, radioactivity levels were 6.2 and 7.0 ng Eq./mL at 8 and 24 hours after administration, respectively.

The applicant explained that the above results suggest that trabectedin and its metabolites can cross the placenta.

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

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

The formation of trabectedin metabolites was investigated by incubating the supernatant obtained by centrifugation of a male human or male monkey liver homogenate, with 5 μmol/L of ^{14}C-labelled trabectedin at 37°C for 120 minutes. The following trabectedin metabolites were obtained both from human and monkey liver samples: ET-729 (*N*-demethylation), 16c (*O*-demethylation), 8a (carboxylic acid formation), 16e (carboxylic acid formation with mono-oxidation), 11a (mono-oxidation), 16b (di-oxidation), 9 (aliphatic ring opening), 4b and 6a (demethylation with mono-oxidation), and 4a, 8c, 16d, and 6b (demethylation with di-oxidation).

The formation of trabectedin metabolites was investigated by incubating ^{14}C-labelled trabectedin with hepatocytes of male mice, male/female rats, male monkeys, or male/female humans at 37°C for 8 or 24 hours (0.03 to 300 nmol/L, or 2 μmol/L of trabectedin for male mouse, female rat, and male monkey hepatocytes; 1 to 100 nmol/L, or 2 μmol/L of trabectedin for male rat and male/female human hepatocytes). The results showed that ET-729 and ET-759A (a carbonyl derivative and a trabectedin degradation product) were detected in male mouse, male monkey, and male/female human samples, while only ET-729 was detected in male/female rat samples.

^{14}C-labelled trabectedin (5 μmol/L) was incubated with human or monkey liver microsomes spiked with uridine diphosphoglucuronic acid in the presence of alamethicin at 37°C for 120 minutes. Glucuronide conjugates of trabectedin were not detected.

Trabectedin (13 nmol/L) was incubated with human liver microsomes at 37°C for 20 minutes in the presence of inhibitors of cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) and antibodies against CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). The residual rate of trabectedin (trabectedin concentration after 20-minute incubation expressed as a percentage of baseline trabectedin concentration) was 82.3% and 85.0% following treatment with ketoconazole and troleandomycin (CYP3A inhibitors), respectively, in contrast to <10% following treatment with inhibitors of other CYP isoforms. As for antibodies against CYP isoforms, the residual rate was 73.9% following treatment with antibodies against CYP3A4, in contrast to <20% following treatment with antibodies against other CYP isoforms.

Based on the above, the applicant considers that CYP3A4 is primarily involved in the metabolism of trabectedin.

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

Trabectedin and its metabolites are mainly excreted in feces via bile in rats [see "3.(ii).A.(4).1) Urinary, fecal, and biliary excretion"]; therefore, biliary metabolites of trabectedin were investigated by

intravenous bolus injection of a single dose of 80 μg/kg of ^{14}C-labelled trabectedin into bile duct-cannulated male and female rats. As a result, ET-729 was mainly detected in both male and female rats.

A single dose of 250 μg/kg of trabectedin was administered intravenously to bile duct-cannulated male and female rats to study biliary metabolites 2 hours after administration. In both male and female rats, the biliary excretion rate was <2% of the total dose for both unchanged trabectedin and ET-729. The biliary excretion of ET-729 was higher in female rats (1.1% of the total dose) than in male rats (0.2% of the total dose) (*Clin Cancer Res.* 2002;8:2952-62). CYP2C and CYP3A are considered to be involved in the metabolism of trabectedin in rats (*Clin Cancer Res.* 2002;8:2952-62), and the expression levels and metabolic activity of these CYP isoforms are higher in male rats than in female rats (*J Vet Med Sci*. 2010;72:471-9). The applicant considers that this may be attributable to the higher biliary excretion in female rats.

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

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

A single dose of 80 μg/kg of ^{14}C-labelled trabectedin was administered intravenously by bolus injection to male and female rats to study the urinary and fecal excretion rates of radioactivity (expressed as a percentage of the dose administered). The total radioactivity recovered within 168 hours after administration was 90.8% in male rats and 93.0% in female rats. The urinary and fecal excretion rates were 2.0% and 71.0% respectively, in male rats, and 4.8% and 43.4%, respectively, in female rats. A single dose of 80 μg/kg of ^{14}C-labelled trabectedin was administered intravenously by bolus injection to bile duct-cannulated male and female rats to study the biliary excretion rate of radioactivity (expressed as a percentage of the dose administered). The biliary excretion rates within 48 hours after administration were 38.6% to 48.8% in male rats and 15.7% to 24.3% in female rats. Metabolite ET-729 [see "3.(ii).A.(3).2) *In vivo* metabolism"], which forms in larger amounts in female rats, induces hepatotoxicity [see "3.(iii).A.(1). Single-dose toxicity" and "3.(iii).A.(2) Repeat-dose toxicity"]. The applicant considers that the hepatotoxicity caused a delay in biliary excretion in female rats, resulting in the lower biliary and fecal excretion in female rats than in male rats in this study.

The applicant considers that, based on the above, trabectedin and its metabolites are mainly excreted in feces via bile in rats.

A single dose of 150 μg/kg of ^{14}C-labelled trabectedin was administered intravenously as a bolus injection to wild-type mice and mdr1a/1b (-/-) mice, to investigate the effects of P-gp on the urinary and fecal excretion of radioactivity (expressed as a percentage of the dose administered). The urinary and fecal excretion rates of radioactivity within 96 hours after administration were 2.3% and 70.6%, respectively, in wild-type mice, and 2.2% and 75.4%, respectively, in mdr1a/1b (-/-) mice, showing no clear differences in urinary and fecal excretion rates between wild-type mice and mdr1a/1b (-/-) mice.

Based on the above results, the applicant considered that P-gp is only slightly involved in the excretion of trabectedin and its metabolites.

3.(ii).A.(4).2) Enterohepatic circulation

In a foreign phase I study (Study ET-A-013-01) [see "4.(ii).A.(2).3) Foreign phase I study"], human fecal samples collected up to 120 hours after administration of ^{14}C-labelled trabectedin were treated with β-glucuronidase. The results showed that there were no significant differences in the radioactivity levels of unchanged trabectedin between β-glucuronidase-treated and untreated samples. However, it is not clear whether the metabolites of trabectedin undergo enterohepatic circulation.

Based on the above results, the applicant considered that trabectedin is unlikely to undergo enterohepatic circulation via glucuronidation.

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

The excretion of trabectedin in breast milk has not been studied. The applicant explained that since it is unknown whether trabectedin is excreted in milk, a cautionary statement will be included in the package insert to warn against breastfeeding during treatment.

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

3.(ii).A.(5).1) *In vitro* enzyme inhibition

The substrates of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) were incubated with human liver microsomes at 37°C for 10 to 30 minutes in the presence of trabectedin (0.01 to 5 μmol/L), to evaluate the inhibitory effects of trabectedin on the CYP isoforms. Trabectedin inhibited metabolism of the substrate for CYP3A (midazolam) with an IC_{50} of 1.5 μmol/L (Ki value, 0.75 μmol/L). In contrast, the IC_{50} of trabectedin for the metabolism of substrates of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 was ≥5 μmol/L. Trabectedin did not show time-dependent inhibition of any of the CYP isoforms studied.

C_{max} of trabectedin was 2.2 nmol/L (1.7 ng/mL) following administration of 1.2 mg/m^2 of trabectedin to Japanese patients with STS by intravenous infusion over 24 hours [see "4.(ii).A.(1).2) Japanese phase II study"]. The applicant therefore considers that trabectedin is unlikely to cause pharmacokinetic drug interactions through inhibition of CYP isoforms in clinical use.

3.(ii).A.(5).2) *In vitro* enzyme induction

Human hepatocytes were treated with trabectedin (1, 5, or 10 nmol/L) for 50 hours, to evaluate the mRNA expression levels of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. After treatment with trabectedin at 1, 5, or 10 nmol/L, the mRNA expression levels of CYP1A1 increased to 1.1-, 2.2-, and 4.9-fold the level of the control, respectively. No significant increase in mRNA expression resulting from the treatment with trabectedin was observed for the rest of the CYP isoforms studied.

C_{max} (concentration of unbound form of trabectedin) following administration of 1.2 mg/m^2 of trabectedin to Japanese STS patients by intravenous infusion over 24 hours was 0.06 nmol/L (0.05 ng/mL) [see "3.(ii).A.(2).2) Plasma protein binding and blood cell distribution" and "4.(ii).A.(1).2) Japanese phase II study"]. The applicant therefore considers that trabectedin is unlikely to cause pharmacokinetic drug interactions through induction of CYP isoforms in its clinical use.

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

The applicant explained that the following study results have demonstrated that trabectedin is a substrate for P-gp.

- Transport of P-gp mediated ^{14}C-labelled trabectedin (218 nmol/L) was investigated using pig kidney cell lines LLC-PK1 expressing human or mouse P-gp. The ratio of basolateral-to-apical transport to apical-to-basolateral transport of ^{14}C-labelled trabectedin (expressed as a percentage of the dose administered) was approximately 2.2, 4.4, and 8.0 in LLC-PK1 cell line, LLC-PK1 cell line expressing human P-gp, and LLC-PK1 cell line expressing mouse P-gp, respectively. In the presence of LY335979 (P-gp inhibitor), this ratio was approximately 0.8, 1.0, and 1.0 in LLC-PK1 cell line, LLC-PK1 cell line expressing human P-gp, and LLC-PK1 cell line expressing mouse P-gp, respectively. The intracellular radioactivity of ^{14}C-labelled trabectedin in LLC-PK1 cell line, LLC-PK1 cell line expressing human P-gp, and LLC-PK1 cell line expressing mouse P-gp were approximately 0.051, 0.015, and 0.01 ng/μg protein, respectively. In the presence of LY335979, the intracellular radioactivity increased approximately 1.7-, 6.4-, and 8.2-fold, respectively, compared with the radioactivity in the absence of LY335979 (*Invest New Drugs.* 2006;25:1-7).
- The tissue-to-plasma ratios of radioactivity $AUC_{0\text{-}96h}$ in the brain and testicle of mdr1a/1b(-/-) mice were 5.9 and 4.0, respectively, which were approximately 11.6- and 1.8-fold the ratios of wild-type mice (0.51 and 2.2, respectively) [see "3.(ii).A.(2).1) Tissue distribution"].

The applicant also stated that based on the following points, co-administration of trabectedin and a P-gp inhibitor is unlikely to cause pharmacokinetic drug interactions.

- Since the route of administration of trabectedin is intravenous, P-gp, expressed in the gastrointestinal tract, is unlikely to affect the PK of trabectedin.
- Following intravenous administration of ^{14}C-labelled trabectedin to patients with solid cancer, the urinary excretion rate of radioactivity was 5.8% of the total dose and unchanged trabectedin represents <1% [see "4.(ii).A.(2).3) Foreign phase I study"]. Given this, the inhibition of P-gp, which is involved in tubular secretion, is unlikely to affect the PK of trabectedin.
- In a Japanese phase I study (Study 10045020) and phase II study (Study 10045030), 1 subject in each study was found to have been receiving trabectedin in combination with clarithromycin (P-gp inhibitor), and no adverse events were reported in these subjects.

The applicant's additional explanation:

Given that the C_{max} (concentration of unbound form of trabectedin) following administration of 1.2 mg/m^2 of trabectedin to Japanese STS patients by intravenous infusion over 24 hours was 0.06 nmol/L (0.05 ng/mL) [see "3.(ii).A.(2).2) Plasma protein binding and blood cell distribution" and "4.(ii).A.(1).2) Japanese phase II study"], together with the results of the study discussed below, administration of trabectedin is unlikely to cause pharmacokinetic drug interactions through inhibition of P-gp, breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, organic anion transporter (OAT) 1, or organic cation transporter (OCT) 2 in its clinical use.

- The inhibitory effects of trabectedin (30 nmol/L) on substrate transport mediated by transporters were investigated using the LLC-PK1 cell line expressing human P-gp, Madin-Darby canine kidney II (MDCK II) cell line expressing human BCRP, and human embryonic kidney (HEK) 293 cell line expressing OATP1B1, OATP1B3, OAT1, or OCT2. Substrates used for transporters were as follows: ^{3}H-labelled verapamil hydrochloride (0.2 μmol/L) as a P-gp substrate, ^{3}H-labelled prazosin hydrochloride (7 nmol/L) as a BCRP substrate, ^{3}H-labelled estrone sulfate (12 nmol/L) as a OATP1B1 substrate, ^{3}H-labelled cholecystokinin-8 (7 nmol/L) as an OATP1B3 substrate, ^{14}C-labelled *p*-aminohippuric acid (2 μmol/L) as an OAT1 substrate, and ^{14}C-labelled tetraethylammonium (1 μmol/L) as an OCT2 substrate. The results showed that trabectedin did not have an obvious inhibitory effect on P-gp, BCRP, OATP1B1, OATP1B3, OAT1, or OCT2.

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

Based on the submitted data and the following discussion, PMDA concluded that the applicant's explanation on the absorption, distribution, metabolism, excretion, and pharmacokinetic interaction of trabectedin was acceptable.

Tissue distribution

The applicant stated that the study of tissue distribution of trabectedin [see "3.(ii).A.(2).1) Tissue distribution"] used male albino rats, and not any colored animals; therefore, accumulation of trabectedin and its metabolites in melanin-containing tissues is unknown.

PMDA's view:

Distribution of trabectedin in melanin-containing tissues has not been studied, and thus it is unknown whether trabectedin has an affinity to melanin. Furthermore, the evaluation of the safety of trabectedin in melanin-containing tissues is limited due to the small number of patients analyzed in the Japanese clinical studies. Therefore, information on adverse events probably related to the distribution of melanin-containing tissues should be continuously collected, and when new data become available, information should be provided to healthcare professionals in an appropriate manner.

3.(iii) Summary of toxicology studies

In the toxicity studies, [redacted] trabectedin and [redacted] trabectedin were used. Given that there were no differences in toxicokinetic (TK) parameters, and no clear differences in the properties and levels of general toxicity between the test substances, it was concluded that the toxicity study using [redacted] trabectedin was also useful for evaluating the safety of [redacted] trabectedin contained in the drug product.

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

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

3.(iii).A.(1).1) Toxicity of a single bolus dose in mice

A single dose of physiological saline (vehicle control) or 100, 150, or 200 μg/kg of [redacted] trabectedin was administered intravenously as a bolus injection to MF1 mice (15 to 30 male mice/group). Necropsies were performed 14, 42, or 56 days after administration.

In the 150 μg/kg group, moribund animals (2 of 15 animals) were sacrificed 22 or 30 days after administration. In the 200 μg/kg group, deaths occurred in 2 of 30 animals on the day following administration, and moribund animals (8 of 30 animals) were sacrificed 1 to 10 days after administration. Findings noted in animals sacrificed moribund or died include bone marrow hypocellular, congestion and coagulative necrosis of the liver, necrosis in various areas in the gastrointestinal tract, thymic weight decreased, and lymphocyte necrosis in the lymph node and spleen. In surviving animals, the following findings were noted: lesions on the tail (injection site), haematocrit decreased, mean cell volume (MCV) decreased, platelet count decreased, and mean cell haemoglobin concentration (MCHC) increased in the ≥100 μg/kg groups. Necropsies of animals in the 200 μg/kg group 14 days after administration showed increased mitotic figures representing damage repair, myocardial necrosis, and extramedullary haemopoiesis. In contrast, no cardiac findings were observed in the necropsies 56 days after administration, and the extramedullary haemopoiesis had resolved.

Based on the findings, the approximate lethal dose was determined to be 100 to 150 μg/kg.

3.(iii).A.(1).2) Toxicity of a single bolus dose in rats

A single dose of 0.05 mol/L-potassium phosphate solution (pH4.0, vehicle control) or 9, 75, or 90 μg/kg of [redacted] trabectedin was administered intravenously as a bolus injection to Fischer 344 rats (n = 10/sex/group). The animals were necropsied 8 or 29 days after administration.

In the 75 and 90 μg/kg groups, 5 females per group died or were sacrificed due to moribund state within 26 days of administration.

The following findings were noted in the ≥75 μg/kg groups: low body weight, red blood cell count decreased, haemoglobin decreased, haematocrit decreased, MCV increased, nucleated erythrocyte increased, white blood cell count decreased, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, bilirubin total increased, and bilirubin direct increased. Findings

noted in the histopathological examination in the ≥75 μg/kg groups include bone marrow hypocellular, inflammation, gland dilation, and epithelial hyperplasia of the colon, necrosis and inflammation of the liver, cholangitis, cells decreased in mesenteric lymph node and spleen, and thymic atrophy.

Based on the above findings, the approximate lethal dose was determined to be >90 μg/kg in males, and 9 to 75 μg/kg in females.

3.(iii).A.(1).3) Toxicity of a single 3-hour continuous infusion in rats (reference data, non-GLP study)

A single dose of 50 or 100 μg/kg of [redacted] trabectedin ([redacted]) was administered to SD rats (n = 3 females/group), and a single dose of 75 or 100 μg/kg of [redacted] trabectedin was administered to SD rats (n = 3 males/group) by intravenous infusion over 3 hours. The animals were necropsied 14 days after administration. The trabectedin formulation used in this study contained [redacted]% of Impurity A.

All animals in the 100 μg/kg group died or were sacrificed moribund 4 to 7 days after administration. Findings noted in these animals include dehydration, swelling of the liver and the adrenal gland, blood-like large intestinal contents, small intestinal wall thinning, swelling of liver sinusoidal cells, erythrophagia in the liver, multifocal hepatocyte degeneration, and intestinal epithelial cell atrophy and ulcer. The major cause of death was determined to be gastrointestinal disorder.

The following findings were noted in the female animals in the 50 μg/kg group: 4 days after administration, reticulocyte count decreased, white blood cell count decreased, eosinophil count decreased, monocyte count decreased, lymphocyte count decreased, neutrophil count decreased, creatinine decreased, blood urea nitrogen (BUN) decreased, bilirubin total increased, triglycerides increased, alkaline phosphatase (ALP) increased, AST increased, ALT increased, and cholesterol increased; 14 days after administration, haematocrit decreased, haemoglobin decreased, eosinophil count decreased, platelet count decreased, MCV increased, mean cell haemoglobin (MCH) increased, reticulocyte count increased, BUN increased, bilirubin total increased, triglycerides increased, ALP increased, AST increased, ALT increased, and cholesterol increased. These changes were more significant than those observed in the male animals in the 75 μg/kg group. Localized necrosis in the liver was observed in the histopathological examination.

The following findings were noted in the male animals in the 75 μg/kg group: 4 days after administration, reticulocyte count decreased, monocyte count decreased, eosinophil count decreased, total protein decreased, creatinine decreased, albumin decreased, and ALP increased; 14 days after administration, reticulocyte count increased, MCV increased, MCH increased, haematocrit decreased, haemoglobin decreased, red blood cell count decreased, eosinophil count decreased, platelet count decreased, bilirubin total increased, triglycerides increased, ALP increased, AST increased, ALT increased, and BUN decreased. Localized necrosis in the liver was observed in the histopathological examination.

Based on the above findings, the maximum tolerated dose (MTD) in the study was determined to be 75 µg/kg in male rats, and 50 µg/kg in female rats. The approximate lethal dose was determined to be 75 to 100 µg/kg in male rats, and 50 to 100 µg/kg in female rats.

3.(iii).A.(1).4) Toxicity of a single 3- or 24-hour continuous infusion in rats

A single dose of physiological saline (vehicle control) or 50 µg/kg of [redacted] trabectedin ([redacted]) was administered to SD rats (n = 10/sex/group) by intravenous infusion over 3 or 24 hours. The animals were necropsied 3 days or 3 weeks after administration. The trabectedin formulation used in this study contained [redacted]% of Impurity A.

The following findings were noted in the 50 µg/kg group: haematocrit decreased, platelet count decreased, white blood cell count decreased, bone marrow hypocellular, ALT increased, AST increased, ALP increased, necrosis hepatocellular, cholangitis acute, biliary hyperplasia, local irritation at the administration site accompanied by necrosis of the vessel wall, swelling of the pancreas, and pancreatic acinar cell necrosis. Bone marrow hypocellular showed reversibility 3 weeks after administration; however, the changes in the liver were not reversible. Vacuolisation of renal cortical tubules, increased intracytoplasmic zymogen granules in the pancreatic acinar cells, and hyperplasia of the spleen were observed 3 weeks after administration.

Hepatotoxicity was more pronounced in females than in males. Rats receiving a 3-hour intravenous infusion showed slightly more pronounced toxicity changes related to the effects on bone-marrow than rats receiving a 24-hour intravenous infusion. C_{max} of trabectedin in the 3-hour infusion group (0.804 ng/mL for males; 0.994 ng/mL for females) was >5-fold the C_{max} of trabectedin in the 24-hour infusion group (0.131 ng/mL for males; 0.188 ng/mL for females). This suggests that increased C_{max} may have led to the exacerbation of toxicity.

Based on the above findings, the MTD in the study was determined to be 50 µg/kg, and the approximate lethal dose was determined to be >50 µg/kg in both males and females.

3.(iii).A.(1).5) Toxicity of a single bolus dose in dogs

A single dose of 0.05 mol/L-potassium phosphate solution (pH4.0, vehicle control) or 10, 27, or 35 µg/kg of [redacted] trabectedin was administered intravenously as a bolus injection to beagle dogs (n = 2/sex/group). The animals were necropsied 8 or 29 days after administration. No deaths occurred.

The following findings were noted in the ≥27 µg/kg groups: decreased food consumption, body weight decreased, decreased body weight gain, white blood cell count decreased, red blood cell count decreased, haemoglobin decreased, haematocrit decreased, reticulocyte count decreased, platelet count decreased, segmented neutrophil count decreased, ALP increased, ALT increased, AST increased, cholangitis acute in the liver, biliary hyperplasia, cholecystitis chronic, bone marrow hypocellular, increased apoptosis in

the pancreas, pancreatic acinar cell atrophy. All the findings were reversible by 29 days after administration except for those of the liver and gall bladder.

Based on the above findings, the MTD in the study was determined to be 27 μg/kg, and the approximate lethal dose was determined to be >35 μg/kg in both males and females.

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

3.(iii).A.(2).1) Toxicity of 5-day repeated dosing in mice

[redacted] trabectedin 40, 60, or 80 μg/kg or 0.05 mol/L-potassium phosphate solution (pH 4.0, vehicle control) were administered intravenously as a bolus injection once daily for 5 days to CD_2F_1 mice (n = 10/sex/group). The animals were necropsied 8 or 22 days after the first dose.

Five deaths occurred 2 to 4 days after administration (1 of 20 animals in the 40 μg/kg group, 2 of 20 animals in the 60 μg/kg group, and 2 of 20 animals in the 80 μg/kg group), and bone marrow hypocellular was observed in these animals.

Findings observed immediately after administration include dyspnoea, ataxia, debility, and convulsion in the ≥40 μg/kg groups. The following findings were noted: in the ≥40 μg/kg groups, red blood cell count decreased, haemoglobin decreased, haematocrit decreased, reticulocyte count decreased, and absolute neutrophil count decreased; in the ≥60 μg/kg groups, absolute segmented neutrophil count decreased; in the 80 μg/kg group, significant decreases in erythroblasts, myelocytes, and megakaryocytes in the bone marrow, and decreased extramedullary hematopoietic cell count in the spleen and liver. At 22 days after administration, the changes in hematology test results returned to the normal levels or exceeded those of the control group, and in the 80 μg/kg group, marrow hyperplasia, and hyperplasia of splenic extramedullary hematopoietic cells were noted; the histopathological changes were reversible.

Based on the above findings, the MTD for the study could not be determined, and the no observed adverse effect level (NOAEL) was determined to be <40 μg/kg/day.

3.(iii).A.(2).2) Toxicity of 3-cycle repeated dosing in rats (every 3 weeks)

Female SD rats (n = 10/group) received a 3-hour intravenous infusion of physiological saline (vehicle control) or [redacted] trabectedin 2.5, 10, 25, or 50 μg/kg every 3 weeks for a total of 3 infusions (=3 cycles). Male SD rats (n = 10/group) received a 3-hour intravenous infusion of vehicle control or 10, 25, 50, or 75 μg/kg of trabectedin every 3 weeks for a total of 3 infusions (=3 cycles). The animals were necropsied 3 or 21 days after the last infusion.

In the 50 μg/kg group, 6 of 20 animals died or were sacrificed moribund on Days 30 to 39 (during the treatment period), and 3 of 20 animals were sacrificed moribund on Days 48 to 52 (after the completion of treatment period). In the 75 μg/kg group, 6 of 10 animals died or were sacrificed moribund on Days

7 to 10 (during the treatment period), and 1 of 10 animals died on Day 54 (after the completion of treatment period). The following findings were noted in the dead or sacrificed animals of the 50 µg/kg group: epithelial atrophy, single cell necrosis, and ulcer of the stomach, duodenal ulcer, necrosis hepatocellular, lymph node atrophy, splenic atrophy, thymic atrophy, degeneration of the testicular seminiferous epithelium, and emergence of spermatid giant cells; a slight delay in the sexual cycle was observed in females.

The following findings were noted: in the ≥2.5 µg/kg groups, red blood cell count decreased, haematocrit decreased, haemoglobin decreased, MCHC decreased, albumin decreased, reticulocyte count increased, ALT increased, necrosis hepatocellular, bile duct proliferation and inflammation, and administration site inflammation and necrosis; in the ≥10 µg/kg groups, creatinine increased, AST increased, lymph node atrophy, and thymic atrophy; in the ≥25 µg/kg groups, body weight decreased, MCV increased, bilirubin total increased, ALP increased, and bone marrow hypocellular; in the ≥50 µg/kg groups, white blood cell count decreased, splenic atrophy, and small intestinal single cell necrosis; and in the 75 µg/kg group, cellular debris in the epididymis. Toxicity was more pronounced in females than in the males.

Based on the above findings, the MTD for the study was determined to be 25 µg/kg/dose, and the NOAEL was determined to be <2.5 µg/kg/dose in females, and <10 µg/kg/dose in males. The trabectedin exposure (AUC) at the MTD was 1.94 ng·h/mL. The free trabectedin exposure (AUC) at MTD (0.09 ng·h/mL) was approximately 0.05-fold the free trabectedin exposure at the clinical dose,* when adjusted for interspecies differences in plasma protein binding.

* In Study 10045030, following administration of 1.2 mg/m^2 of trabectedin to Japanese STS patients as a 24-hour intravenous infusion, the AUC_{inf} was 66.0 ng·h/mL, and the AUC of free trabectedin was 1.80 ng·h/mL. The plasma protein binding was 95.3% in rats and 97.3% in humans.

3.(iii).A.(2).3) Toxicity of 5-day repeated dosing in dogs (reference data, non-GLP study)

Beagle dogs (n = 2/sex/group) received an intravenous bolus injection of 0.05 mol/L-potassium phosphate solution (pH4.0, vehicle control) or [redacted] trabectedin 5, 8, or 11 µg/kg once daily for 5 days. The animals were necropsied 11 or 36 days after the first dose (recovery period of 6 or 31 days).

The following findings were noted: in the 5 µg/kg group, bone marrow hypocellular, administration site haemorrhage and oedema, hepatic glycogen decreased, and biliary hyperplasia; in the ≥8 µg/kg groups, platelets decreased, white blood cell count decreased, ALP increased, ALT increased, AST increased, gamma-glutamyltransferase increased, cholesterol increased, total protein decreased, albumin decreased, bone marrow hypocellular, decreased lymphocytes in the thymus and lymph nodes, periportal subacute inflammation and oedema in the liver, and gallbladder oedema formation and subacute inflammation; and in the 11 µg/kg group, decreased body weight and decreased food consumption.

At 36 days after the first dose, the following findings were noted: changes at the administration site in the ≥5 µg/kg groups; and pancreatic acinar cell atrophy in the 11 µg/kg group. Decreased lymphocytes in the lymph nodes, bone marrow hypocellular, and hepatic changes were reversible.

Based on the above findings, the NOAEL for the study was determined to be <5 µg/kg/day.

3.(iii).A.(2).4) Toxicity of 3- or 4-cycle repeated dosing in monkeys (every 1 or 3 weeks)

Cynomolgus monkeys (n = 2/sex/group) received a 3-hour intravenous infusion of physiological saline (vehicle control) or 10, 20, or 30 µg/kg of [redacted] trabectedin ([redacted]) for a total of 3 infusions (=3 cycles). Each cycle consisted of once weekly infusion for 3 weeks, followed by a 1-week recovery period. Other cynomolgus monkeys received a 3-hour intravenous infusion of [redacted] trabectedin 70 µg/kg every 3 weeks for a total of 4 infusions (=4 cycles).

One of 4 animals in the 70 µg/kg group died within 2 hours of the first dose, and 2 of 4 animals were sacrificed moribund 38 or 66 days after the first dose. Findings noted in animals that died or were sacrificed moribund include body temperature increased, severe anaemia, white blood cell decreased, fibrinogen increased, AST increased, ALT increased, bone marrow hypocellular in the sternum, decreased lymphocytes in the thymus and lymph nodes, localised ulcer in the gastrointestinal tract, adhesion of the duodenum to other parts of the intestinal tract, cecum dilatation with cecal mucosa necrosis/haemorrhage, and dilatation of tubules with flattened epithelium.

In the ≥10 µg/kg groups, anaemia, myeloid component decreased, erythroblast component increased, and myeloid-to-erythroblast ratio decreased were noted; after the first administration cycle, transient increases in AST, ALT, creatine phosphokinase (CPK), and lactate dehydrogenase were observed, but subsequently returned to the normal range. In the 20 and 30 µg/kg groups, decreased thymic lymphocytes were observed.

In this study, it was concluded that the once-a-week regimen (30 µg/kg/dose) was better tolerated than the every-3-week regimen (70 µg/kg/dose).

3.(iii).A.(2).5) Toxicity of 4-cycle repeated dosing in monkeys (every 3 weeks) (reference data, non-GLP study)

Cynomolgus monkeys (n = 3 or 5/sex/group) received a 24-hour intravenous infusion of physiological saline (vehicle control) or 25, 50, or 70 µg/kg of [redacted] trabectedin ([redacted]) every 3 weeks for a total of 4 infusions (= 4 cycles). Originally, a total of 8 cycles was planned; however, it was decided to terminate the study 3 weeks after the completion of Cycle 4, because it was judged unethical to continue the study after multiple animals were sacrificed moribund during Cycle 3 and thereafter, and even among surviving animals, notable changes at the injection site occurred.

Serious necrotic lesions at the injection sites were observed in Cycle 3 and thereafter, resulting in moribund sacrifice of 2 of 6 animals in the 50 μg/kg group and 4 of 10 animals in the 70 μg/kg group. Furthermore, due to worsening of clinical signs, 1of 10 animals of the 70 μg/kg group was sacrificed moribund. Because of the small number of surviving animals, it was judged difficult to perform appropriate toxicological evaluation and TK evaluation.

In the ≥25 μg/kg groups, the following findings were noted: fibrinogen increased, platelets increased, and inorganic phosphorus decreased. The following findings were noted more frequently with greater severity in the ≥25 μg/kg groups than in the control group: thickening and induration of administration site, vein wall and perivenous inflammation, and degeneration and necrosis at the administration site; and bone marrow hypocellular in the sternum. In the ≥50 μg/kg groups, anaemia, ureteric dilatation, pale kidney, and enlargement of the kidney were noted. In the 70 μg/kg group, BUN increased, creatinine increased, thymic lymphocytes decreased, thymus size diminished, and immature testis were noted. The renal changes were considered to be secondary changes associated with severe thrombophlebitis in the vein cannulated for trabectedin infusion.

Based on the results, it was concluded that a 4-cycle administration of trabectedin 25 μg/kg/dose was tolerable.

* [redacted]

3.(iii).A.(2).6) Toxicity of 4- to 8-cycle repeated dosing in monkeys (every 3 weeks)

Cynomolgus monkeys (n = 3 or 5/sex/group) received a 3-hour intravenous infusion of physiological saline (vehicle control) or [redacted] trabectedin 25, 50, or 65 μg/kg, using a central venous catheter in the vena cava, every 3 weeks for a total of 4 infusions (=4 cycles) or 8 infusions (=8 cycles). The animals were necropsied 3 or 8 weeks after the last infusion. The catheter was placed in the inferior vena cava near the kidney via the femoral vein. Since some animals died or were sacrificed moribund in the 50 and 65 μg/kg groups, surviving animals in these groups were necropsied 8 weeks after the completion of Cycle 4 administration. Furthermore, 35 μg/kg of trabectedin was administered to some of the animals in the control group (n = 3/sex/group) once in a 3-week treatment cycle, for a total of 6 cycles, as a 3-hour intravenous infusion using a central venous catheter in the vena cava. The animals were necropsied 144 hours after the last infusion.

One of 6 animals in the 35 μg/kg group died after receiving 5 doses (day 87). The number of animals that died or were sacrificed moribund were as follows: in the 50 μg/kg group, 2 of 6 animals on days 37 to 42, and 1 of 10 animals after receiving 4 doses; and in the 65 μg/kg group, 1 of 10 animals on day 12, and 7 of 10 animals after receiving 4 doses. In animals that died or were sacrificed moribund before receiving 4 doses, the following findings were observed: white blood cell decreased, atrophy of lymph node and bone marrow, and findings indicative of systemic bacterial infection (gastrointestinal

inflammation, necrosis, and haemorrhage accompanied by bacterial foci, and bacterial foci at the administration site, lung, heart, liver, and other sites). Bacterial-mediated lesions induced by immunosuppression were considered to have caused the deterioration in clinical signs or death. In contrast, in animals that died or were sacrificed at or after administration of the fourth dose, the following findings were observed: leukocytosis, and inflammatory, fibrotic and necrotic changes covering a wide area around the administration site (the inferior vena cava near the kidney), including the ureter, kidney, liver, abdominal muscles, diaphragm, blood vessels, and nerves; and these changes were considered to have caused the deterioration in clinical signs or death.

Localised retinal oedema was observed in the left eye of 1 male in the 25 μg/kg group after the last infusion (Cycle 8); and in the left eye of 1 female in the 35 μg/kg group during Cycle 4, and in the right eye of the same female after the last infusion (Cycle 6). Recovery was not evaluated in these cases because these findings were observed after the last infusion.

The following findings were noted in the ≥25 μg/kg groups: limb activity limitations, hypotonia, and swelling in the limb, finger, lumbar region (genitourinary side), abdominal region, and chest region accompanied by abnormal gait; around the administration site (the inferior vena cava near the kidney), thrombotic occlusion of blood vessel lumen, extensive perivascular inflammation and fibrosis, vascular/perivascular necrosis, and formation of a mass comprising tissues around the administration site (e.g., the ureter, kidney, liver, abdominal muscles, diaphragm, blood vessels, and nerves); hepatic sinusoidal phagocytes and inflammatory cells, interstitial inflammation accompanied by renal fibrosis, tubular basophilia and dilatation, renal pelvis dilatation, dermal or subcutaneous oedema, and degranulation of pancreatic acinar cells. In the ≥35 μg/kg groups, decreased albumin was noted, and based on this finding, the applicant considered that swelling of the limb and reproductive organ region was likely to be caused by hypoalbuminaemia due to decreased kidney function. In the ≥50 μg/kg groups, white blood cell count decreased, and neutrophil count decreased were observed by the end of Cycle 3; and white blood cell count increased and neutrophil count increased were observed after the completion of Cycle 4. Anaemia was also observed during the treatment period. However, these changes had resolved in the surviving animals by the end of the recovery period.

At the end of the recovery period, lesions in the kidney and administration site were observed.

Based on the above, the MTD for the study was determined to be 25 μg/kg/dose, and the NOAEL was determined to be <25 μg/kg/dose. The trabectedin exposure (AUC) at the MTD was 9.20 ng·h/mL. The free trabectedin exposure (AUC) at MTD (0.52 ng·h/mL) was approximately 0.29-fold the free trabectedin exposure at the clinical dose,* when adjusted for the interspecies differences in plasma protein binding.

* In Study 10045030, following administration of 1.2 mg/m^2 of trabectedin to Japanese STS patients as a 24-hour intravenous infusion, the AUC_{inf} was 66.0 ng·h/mL, and the AUC of free trabectedin was 1.80 ng·h/mL. The plasma protein binding was 94.4% in monkeys and 97.3% in humans.

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

Genotoxicity studies were conducted using [redacted] trabectedin. The results of these studies showed that trabectedin is genotoxic.

- In a bacterial reverse mutation assay, a positive response was obtained in the presence of metabolic activation in *Salmonella typhimurium* strain TA100.
- In a chromosomal aberration assay in Chinese hamster ovary (CHO) cells, a positive clastogenic response was detected.
- In a mouse micronucleus assay, 1.5 to 300 µg/kg/day of trabectedin were administered intravenously as a bolus injection, to evaluate the frequency of micronucleated bone marrow polychromatic erythrocytes (MNPCE). The results showed that MNPCE increased in the ≥75 µg/kg/day groups, and the increases in the ≥150 µg/kg/day groups were statistically significant. The estimated AUC for the 75 µg/kg/day group (34.6 ng·h/mL; free trabectedin, 0.38 ng·h/mL)[*1] was lower than the exposure[*2] at the clinical dose. It was thus concluded that the clinical use of trabectedin has a risk of causing chromosomal aberrations.

*1, values estimated from the AUC (92.3 ng·h/mL) in mice receiving a single dose of 200 µg/kg of trabectedin.

*2, In Study 10045030, following administration of 1.2 mg/m^2 of trabectedin to Japanese STS patients as a 24-hour intravenous infusion, the AUC_{inf} was 66.0 ng·h/mL, and the AUC of free trabectedin was 1.80 ng·h/mL. The plasma protein binding was 98.9% in mice and 97.3% in humans.

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

No carcinogenicity studies were conducted because trabectedin is used for the treatment of STS. The results of the genotoxicity studies, however, suggested that trabectedin is genotoxic [see "3.(iii).A.(3) Genotoxicity"]; therefore, it was concluded that there was a risk of second primary cancer associated with administration of trabectedin in the clinical setting.

3.(iii).A.(5) Reproductive and developmental toxicity

Embryo-fetal development studies in rats and rabbits were conducted to evaluate the reproductive and developmental toxicity. No studies have been conducted to evaluated fertility and early embryonic development to implantation, or on the effects on pre- and postnatal development, including maternal function, because trabectedin is used for the treatment of STS. The results from the rat study suggested that trabectedin can cross the placental barrier [see "3.(ii).A.(2).3) Placental transfer and fetal distribution"].

3.(iii).A.(5).1) Effects on fertility

Although no studies have been conducted to evaluate fertility and early embryonic development to implantation, it was concluded that administration of trabectedin would be likely to affect male/female reproductive cell formation and male/female fertility for the following reasons: (a) in the repeat-dose toxicity study in rats [see "3.(iii).A.(2).2) Toxicity of 3-cycle repeated dosing in rats (every 3 weeks)"],

degeneration of the testicular seminiferous epithelium, emergence of spermatid giant cells, and cellular debris in the epididymis were observed; (b) a delay in the sexual cycle was observed in female rats; (c) positive responses were obtained in all genotoxicity studies conducted [see "3.(iii).A.(3) Genotoxicity"]; and (d) trabectedin is cytotoxic. With regard to immature testis observed in the repeat-dose toxicity study in monkeys [see "3.(iii).A.(2).5) Toxicity of 4-cycle repeated dosing in monkeys (every 3 weeks)"], the applicant considered that the occurrence of immature testis could have been incidental in animals that had not reached reproductive maturity, based on the fact that the animals used in the study were ≥2 years of age. Given that animals that had not reached reproductive maturity might have been included in the monkey repeat-dose toxicity studies, it is difficult to evaluate fertility accurately based on the results of the studies.

Based on the above, the applicant explained that appropriate cautions, especially with regard to the effects on fertility, are required when using trabectedin in the clinical setting; in male patients, use of contraception is required during the treatment with trabectedin and also for a certain period after the completion of treatment.

3.(iii).A.(5).2) Embryo-fetal development study in rats (reference data, non-GLP study)

Physiological saline (vehicle control) or 0.1, 0.5, or 2.5 μg/kg of [redacted] trabectedin were administered intravenously once daily as a bolus injection to pregnant SD rats (n = 25/group) on gestation days 6 to 17. In dam animals, body weight decreased (from gestation day 10) and food consumption decreased (from gestation day 12) were observed in the 2.5 μg/kg group. In embryos and fetuses, mild degree of low body weight was observed in the ≥0.5 μg/kg groups.

Based on the above, the NOAEL for the study was determined to be 0.5 μg/kg/day for maternal toxicity, and 0.1 μg/kg/day for embryonic and fetal development toxicity.

3.(iii).A.(5).3) Embryo-fetal development study in rabbits (reference data, non-GLP study)

Physiological saline (vehicle control) or 0.3, 0.75, or 2 μg/kg of [redacted] trabectedin were administered intravenously once daily as a bolus injection to pregnant New Zealand white (NZW) rabbits (n = 20/group) on gestation days 7 to 20. In dam animals, administration site irritation was observed in the ≥0.75 μg/kg groups, and food consumption decreased in the 2 μg/kg group; but no effects on embryonic or fetal development were observed.

Based on the above results, the NOAEL for the study was determined to be 0.3 μg/kg/day for maternal toxicity, and 2 μg/kg/day for embryonic and fetal development toxicity.

The applicant's explanation:

No embryonic and fetal development toxicity including teratogenicity was observed in the above embryo-fetal development studies in rats and rabbits except for a slightly lower body weight. Because of maternal dose limiting toxicity (DLT), the dose and exposure in these studies were much lower than

the clinical dose and exposure. Therefore, the risk associated with trabectedin in pregnant patients cannot be adequately evaluated based on these study results. Trabectedin should be contraindicated in pregnant women because of potential embryonic and fetal toxicity based on the following: (a) trabectedin binds to DNA, and has cytotoxicity [see "3.(i).A.(1).1) Pharmacological characteristics"]; (b) positive responses were obtained in genotoxicity studies [see "3.(iii).A.(3) Genotoxicity"]; and (c) trabectedin was shown to cross the placental barrier into the fetus [see "3.(ii).A.(2).3) Placental transfer and fetal distribution"].

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

3.(iii).A.(6).1) Intravenous and paravenous administration study in rabbits

A single dose of 2.5 or 25 μg/mL of [redacted] trabectedin ([redacted]) was administered to the auricle of NZW rabbits (n = 4 males/group) intravenously (1.0 mL) or into paravenous tissue (0.3 mL). Within 72 hours of administration into paravenous tissue, swelling, erythema, haematoma, vasodilatation, ulcer, localised fibrinoid necrosis, epithelial necrosis, subacute inflammation, and oedema were observed at the administration site. Animals receiving trabectedin intravenously showed administration site swelling and erythema, with the severity being lower in the 2.5 μg/mL group than in the 25 μg/mL group. In the 25 μg/mL intravenous administration group, localised fibrinoid necrosis, epithelial necrosis, subacute inflammation, and oedema were observed.

3.(iii).A.(6).2) Local tolerance/tissue reactivity study in rabbits

NZW rabbits (n = 10 females/group) received a single dose or repeated doses (once weekly for 4 weeks) of 0.3 mL/kg (at 7 μg/mL concentration, the same as the clinical concentration) of [redacted] trabectedin ([redacted]) or [redacted] trabectedin ([redacted]) into the peripheral vein in the auricle. The animals were necropsied 3 days after the single administration, or 3 days after the last dose of the repeated administration, to evaluate local tolerance and tissue reactivity. In animals that received multiple doses, mild erythema, and slight to mild vascular disorder in the peripheral vein region in the auricle were noted in both the [redacted] trabectedin and [redacted] trabectedin groups. No differences in irritability between the formulations were observed.

Based on the observation of local irritation at the administration site in the above studies in 3.(iii).A.(6).1) and 3.(iii).A.(6).2), and repeat-dose toxicity studies in monkeys [see "3.(iii).A.(2).6) Toxicity of 4- to 8-cycle repeated dosing in monkeys (every 3 weeks)"], the applicant stated that close attention should be paid to extravasation-related adverse events in clinical use, because when trabectedin is extravasated from the venous lumen into the perivascular tissue, trabectedin may be retained within the tissue, and bind to DNA, causing persistent tissue disorder, in addition to causing tissue disorder resulting from the physicochemical characteristics of trabectedin.

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

3.(iii).A.(7).1) Mechanism of liver toxicity

i) Comparative cytotoxicity in hepatocytes from 4 animal species (reference data, non-GLP study)

^{14}C-labelled [redacted] trabectedin 0.03 nmol/L to 2 µmol/L was added to primary hepatocyte cultures isolated from male mice, male/female rats, male monkey or male/female humans, to evaluate cytotoxicity 8 or 24 hours later. In the mouse and human hepatocytes, cytotoxicity was observed 24 hours later at 10 nmol/L. In the rat and monkey hepatocytes, cytotoxicity was observed 24 hours later at 100 nmol/L.

ii) Cytotoxicity of trabectedin and its metabolite, ET-729, in hepatocytes, liver cancer cells, and other cell lines (reference data, non-GLP study)

[redacted] trabectedin 1 nmol/L to 2 µmol/L or its metabolite ET-729 were added to primary hepatocyte cultures isolated from male mice, male/female rats, male monkeys or male/female humans, and to hepatoma cell line HepG2. The cytotoxicity was evaluated after 24-hour exposure, or 48 hours after the washout of the test substance after 24-hour exposure. No obvious differences in cytotoxicity were observed between trabectedin and ET-729. In all cells, more significant cytotoxicity was observed 48 hours after the washout of the test substance compared to that of after 24-hour exposure. The mouse hepatocytes and female rat hepatocytes were the most sensitive to trabectedin and ET-729. The sensitivity to trabectedin or ET-729 was higher in the female rat cells than in the male rat cells.

iii) Alleviation of liver toxicity in rats by high-dose dexamethasone (reference data: *Cancer Res* 2003; 63: 5902-08)

The possibility of reducing the occurrence of trabectedin-induced hepatotoxicity through pretreatment with dexamethasone (DEX) was investigated. A single dose of 40 µg/kg of [redacted] trabectedin was administered intravenously as a bolus injection to Wistar rats (n = 5 females/group), with one group receiving an oral dose of 10 mg/kg of DEX 24 hours before trabectedin administration, and the other group not undergoing pretreatment. The non-DEX-pretreatment group showed ALP increased, AST increased, bilirubin increased, and degeneration and spotty localised necrosis of biliary epithelial cells. In contrast, in the DEX-pretreatment group, these changes were either reduced or not observed. Although no significant differences in the concentration of trabectedin in plasma were observed between the groups, the concentration of trabectedin in the liver did not exceed 5 pmol/g tissue in the DEX-pretreatment group, while the concentration of trabectedin in the liver was 37 pmol/g tissue in the non-DEX-pretreatment group.

The above results suggested that pretreatment with DEX can reduce trabectedin-induced hepatotoxicity in rats. The applicant considers that pretreatment with DEX may reduce trabectedin-induced hepatotoxicity in the clinical setting.

3.(iii).A.(7).2) Comparison of maximum tolerated doses (MTDs) for a single dose of ET-729 in mice (reference data, non-GLP study)

A single dose of 200, 225, 250, or 300 μg/kg of [redacted] trabectedin or 75, 100, 125, or 150 μg/kg of ET-729 was administered intravenously as a bolus injection to CD-1 mice (n = 5/sex/group). Among animals that received trabectedin, 1 of 10 animals died (male) in the 250 μg/kg group, and 5 of 10 animals died in the 300 μg/kg group 8 to 13 days after administration. Among animals that received ET-729, 5 of 10 animals died in the 125 μg/kg group, and 9 of 10 animals died in the 150 μg/kg group.

Based on the above results, the MTD of trabectedin was determined to be 225 μg/kg in males, and 250 μg/kg in females. The MTD for ET-729 was determined to be 100 μg/kg.

3.(iii).A.(7).3) Safety evaluation of impurities

Impurities A, B, C, D, E, and F are contained in the drug substance at [redacted]%, i.e., higher concentrations than the acceptable threshold (meaning that a safety assessment is required). These impurities were shown to be safe in the following studies.

i) General toxicity of impurities

The following 3 studies were conducted to evaluate general toxicity of impurities. All studies used dose levels exceeding the maximum daily impurity intake in the clinical setting.

- Toxicity study of single intravenous administration in rats: Impurity B ([redacted]%) was co-administered with [redacted] trabectedin (Study [redacted])
- Toxicity study of single intravenous administration in rats[*1]: Impurities C ([redacted]%), and F ([redacted]%) were co-administered with [redacted] trabectedin (Study [redacted])
- Study of single intravenous administration in rats[*2]: Impurity D ([redacted]%), E ([redacted]%), or A ([redacted]%) was added to [redacted] trabectedin and administered to rats (Study [redacted]).

*1, Impurity A was contained at [redacted]% in trabectedin used for the study.

*2, [redacted]

These studies showed that the toxicity of trabectedin plus an impurity co-administered or added (other than Impurity A) was similar to the toxicity of trabectedin alone. These impurities (other than Impurity A) were thus shown to be safe in terms of general toxicity.

In Study [redacted], in the group that received Impurity A ([redacted]%) added to trabectedin, bone marrow suppression and changes at the administration site caused by local irritation were worse compared with the group that received trabectedin alone, and further, gait stumbling and death occurred, which were not observed in the group that received trabectedin alone. However, when the following points are taken into consideration, it was concluded that Impurity A was safe up to [redacted]% (the specification value) in the drug substance.

- In the toxicity studies where rats received a single continuous intravenous infusion [see "3.(iii).A.(1).3) Toxicity of a single 3-hour continuous infusion in rats" and "3.(iii).A.(1).4) Toxicity of a single 3- or 24-hour continuous infusion in rats"], the drug substance contained Impurity A at [redacted]%. In the toxicity study (Study [redacted]) of Impurities C and F, the drug substance contained Impurity A at [redacted]%. The dose level of Impurity A in the trabectedin 50 µg/kg group in the studies, [redacted]µg/kg, is higher than the maximum daily intake ([redacted]µg/kg) in the clinical setting.
- In the toxicity studies where rats received a single continuous intravenous infusion [see "3.(iii).A.(1).3) Toxicity of a single 3-hour continuous infusion in rats" and "3.(iii).A.(1).4) Toxicity of a single 3- or 24-hour continuous infusion in rats"], and the toxicity study (Study [redacted]) in which the toxicity of Impurities C and F was evaluated, no deaths occurred in the trabectedin 50 µg/kg group; furthermore, the toxicity in the group that received trabectedin alone (50 µg/kg) in Study [redacted] and the toxicity in the above 2 toxicity studies of single continuous intravenous infusion were similar.
- The dose level for Impurity A in Study [redacted] was [redacted]µg/kg, while the maximum daily intake of Impurity A in the clinical setting is [redacted]µg/kg.

ii) Genotoxicity of impurities

The results of *in silico* evaluation of the genotoxicity of Impurities A, B, C, D, E, and F using two structural activity relationship software programs (Derek Nexus and MultiCASE) did not suggest that any of these impurities were associated with a risk of genotoxicity. Furthermore, given that the total maximum intake of the 6 impurities in a clinical dose is 33.1 µg, and that trabectedin is administered once every 3 weeks, it was concluded that there was no basis for concerns regarding the genotoxicity of impurities in the clinical use of trabectedin.

3.(iii).A.(7).4) [redacted]

SD rats (n = 10/sex/group) received 50 µg/kg of [redacted] trabectedin ([redacted]), [redacted] trabectedin ([redacted]), or forcefully degraded [redacted] trabectedin ([redacted]) as a 3-hour intravenous infusion. The animals were necropsied 3 days or 3 weeks after administration.

In all groups, the following findings were noted: anaemia, lymphocyte count decreased, monocyte count decreased, bilirubin increased, cholesterol increased, triglyceride increased, AST increased, ALT increased, urine occult blood, urinary bilirubin increased, liver weight increased, and lymph node weight increased, thymic weight decreased, splenic weight decreased, and administration site irritation with lymph nodes enlarged. There were no significant differences in toxicity between treatment groups.

* [redacted]

3.(iii).A.(7).5) Photosafety

There is no maximum absorption in the wavelength range of 290 to 700 nm in the optical absorption spectrum for trabectedin; therefore, it was concluded that the risk with respect to photosafety was low, and no phototoxicity studies have been conducted. In Japanese clinical studies (Studies 10045020, 10045030, and 10045040), no adverse events considered to be attributable to photosensitivity or photoallergic reactions were observed in patients (n = 73) who received 1.2 mg/m^2 of trabectedin every 3 weeks. Moreover, no preferred terms suggesting photoallergic reactions were found in the adverse events reported in EU post-marketing surveillance programs from September 2007, when trabectedin was approved, to September 2014.

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

PMDA concluded that the evaluation of non-clinical toxicity revealed no problems associated with the clinical use of trabectedin based on the submitted data and the following discussion.

Retinal oedema

Given that retinal oedema was observed in the repeat-dose toxicity study in monkeys [see "3.(iii).A.(2).6) Toxicity of 4- to 8-cycle repeated dosing in monkeys (every 3 weeks)"], PMDA asked the applicant to explain the risk of retina-related adverse events in the clinical use of trabectedin.

The applicant's response:

It cannot be ruled out that the retinal oedema observed in the repeat-dose toxicity study in monkeys may be related to trabectedin, taking the following points into consideration:

- Retinal oedema is unlikely to develop in monkeys from natural causes.
- The distribution of trabectedin in the eye was confirmed in the rat study [see "3.(ii).A.(2).1) Tissue distribution"], therefore, it is considered possible that trabectedin can also be distributed in the eye.
- Trabectedin is a cytotoxic agent.

However, in the animal in which retinal oedema was observed, renal pelvis dilatation of the kidney, ureteric dilatation, and oedema in the subcutaneous tissue were also observed; therefore, retinal oedema is likely to be related to decreased renal function.

Based on the above, the risk of retina-related adverse events in the clinical use of trabectedin is considered to be low.

PMDA's view:

Because it cannot be ruled out that a relationship could exist between retinal oedema and the administration of trabectedin in the repeat-dose toxicity study in monkeys, and for other reasons, the potential risk of causing retina-related adverse events exists when administering trabectedin. Therefore, it is necessary to provide information on retinal oedema observed in the repeat-dose toxicity study in monkeys by including a cautionary statement in the package insert.

4. Clinical data

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

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

Trabectedin in human plasma was quantitated by liquid chromatography-tandem mass spectrometry, and the lower limit of quantitation was 10 to 25 pg/mL.

4.(ii) Summary of clinical pharmacology studies

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

The pharmacokinetics (PK) of trabectedin administered alone and in combination with ketoconazole (KCZ), rifampicin (RFP), or dexamethasone (DEX) in cancer patients was studied.

4.(ii).A.(1) Japanese clinical studies

4.(ii).A.(1).1) Japanese phase I study (5.3.3.2.1, Study 10045020 [September 2010 to July 2013])

An open-label, uncontrolled study was conducted in 15 patients (15 patients included in the PK analysis) with unresectable soft tissue sarcoma (STS) previously treated with chemotherapy, to investigate the PK and other parameters of trabectedin.

In this 21-day cycle study, subjects received an intravenous administration of 20 mg of DEX, and at least 30 minutes later, a 24-hour intravenous infusion of 0.9, 1.2, or 1.5 mg/m^2 of trabectedin, every 3 weeks. Plasma concentrations were evaluated (see table below).

In the dose range studied, C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} were not dose proportional, and the applicant explained that this could be attributable to inter-subject variation.

Pharmacokinetic parameters of trabectedin following the first dose

Dose (mg/m^2)	n	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	t_{max}*1 (h)	CL (L/h)	$V_{d,ss}$ (L)
0.9	3	1.6 ± 1.0	46.9 ± 17.3	77.7 ± 31.8	221 ± 126	23.9 (1.5, 24.2)	21.0 ± 11.7	3790 ± 1810
1.2	9	2.1 ± 3.0	53.9 ± 25.3	74.9 ± 42.7	124 ± 35	24.0 (1.5, 26.9)	31.4 ± 9.5	3380 ± 1050
1.5	3	2.0 ± 0.7	96.3 ± 29.0	116, 147*2	81.0, 266*2	24.1 (1.5, 24.2)	18.2, 24.0*2	1940, 5660*2

Mean ± SD; *1, median (range); *2, individual values (n = 2)

4.(ii).A.(1).2) Japanese phase II study (5.3.5.1.1, Study 10045030 [ongoing since July 2012, data cut-off on February 8, 2014])

A randomized, open-label, comparative study was conducted in 76 patients (37 patients included in the PK analysis) previously treated with chemotherapy for unresectable soft tissue sarcoma (STS) of histological subtypes reported to carry chromosomal translocations [see "4.(iii).A. Evaluation data (1).2) Japanese phase II study"], to investigate the PK and other parameters of trabectedin.

In this 21-day cycle study, subjects received an intravenous administration of 20 mg of DEX, and at least 30 minutes later, a 24-hour intravenous infusion of 1.2 mg/m^2 of trabectedin, every 3 weeks; and plasma concentrations were evaluated (see table below).

Pharmacokinetic parameters of trabectedin following the first dose

n	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	t_{max}*1 (h)	CL (L/h)	$V_{d,ss}$ (L)
37	1.7 ± 1.7	57.6 ± 39.7	66.0 ± 24.7*2	107 ± 29*2	24.3 (1.5, 27.2)	34.3 ± 10.4*2	3040 ± 1170*2

Mean ± SD; *1, median (range); *2, n = 33

The relationship between the plasma concentrations of α1-acid glycoprotein and the PK parameters of trabectedin obtained in the Japanese phase II study (10045030) was also investigated, because trabectedin binds to α1-acid glycoprotein [see "3.(ii).A.(2).2) Plasma protein binding and blood cell distribution"]. The results showed that the plasma concentration of α1-acid glycoprotein was correlated positively with C_{max}, AUC_{0-t}, and AUC_{inf}, and negatively with CL and Vd,ss. The applicant explained that, given that trabectedin is primarily eliminated by hepatic metabolism [see "4.(ii).A.(2).3) Foreign phase I study"], fluctuation of α1-acid glycoprotein in plasma would not be likely to affect the concentration of free trabectedin in blood in clinical use.

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

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2.2, Study ET-A-002-95 [May 1996 to June 1999])

An open-label, uncontrolled study was conducted in 52 patients with solid cancer (52 patients included in the PK analysis) to investigate the PK and other parameters of trabectedin.

In this 21-day cycle study, subjects received doses of 0.05 to 1.8 mg/m^2 of trabectedin as a 24-hour intravenous infusion, every 3 weeks; and plasma concentrations were evaluated (see table below).

In the dose range studied, C_{max}, and AUC_{inf} were not dose proportional, and the applicant explained that this could be attributable to inter-subject variation. The applicant attributed the large variations in the mean values of $t_{1/2}$, CL, and V_z to low plasma concentrations of trabectedin at lower doses, which could have prevented accurate estimation of the final phase values.

No clear differences were observed in C_{max}, AUC_{inf}, or CL in the dose range of 1.2 to 1.8 mg/m^2 of trabectedin between cycles 1 and 2.

Pharmacokinetic parameters of trabectedin

Dose (mg/m^2)	Cycle	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	t_{max}*1 (h)	CL (L/h)	V_z (L)
0.05*2	1	3	0.06 ± 0.04	1.2 ± 0.7	8.9 ± 10.6	24.0 (23.5, 24.5)	82.3 ± 41.9	629 ± 419
0.1*2		3	0.08 ± 0.05	2.3 ± 1.9	27.9 ± 34.3	24.2 (6.1, 24.6)	110.5 ± 73.7	2165 ± 1320
0.2*2		3	0.2 ± 0.08	3.8 ± 1.5	26.4 ± 18.2	24.3 (23.5, 24.9)	103.9 ± 46.2	3435 ± 1769

0.4[*2]		3	0.8 ± 0.5	23.5 ± 18.3	30.7 ± 20.1	23.6 (23.5, 23.9)	41.5 ± 21.8	1425 ± 180
0.6[*2]		3	0.6 ± 0.2	12.0 ± 4.5	20.6 ± 14.0	24.4 (23.5, 25.1)	94.4 ± 51.5	3484 ± 3882
0.9[*2]		3	0.9 ± 0.2	28.4 ± 4.5	29.4 ± 10.1	6.1 (2.3, 23.6)	62.0 ± 10.4	2546 ± 541
1.2	1	5	1.4 ± 0.6	33.5 ± 14.0	36.8 ± 17.0	23.7 (23.5, 24.1)	74.4 ± 34.5	3915 ± 2073
	2	4	1.4 ± 0.9	34.6, 44.5[*3]	55.9, 35.1[*3]	6.0 (2.0, 23.6)	62.1, 44.7[*3]	5011, 2264[*3]
1.5	1	24[*4]	1.8 ± 1.1[*5]	56.8 ± 24.9	103.2 ± 41.8	24.1 (2.0, 26.5)[*5]	54.7 ± 23.5	7509 ± 3412
	2	20	1.7 ± 1.4	58.1 ± 49.0	77.4 ± 57.3	23.5 (2.0, 25.6)	71.0 ± 51.2	5655 ± 3142
1.8	1	4	2.8 ± 1.4	60.2 ± 24.5	91.8 ± 27.9	24.3 (5.8, 24.7)	57.4 ± 28.7	8369 ± 7032
	2	4	1.1 ± 0.07	65.7 ± 24.5	126.0 ± 46.9	23.4 (6.2, 23.5)	47.4 ± 12.0	8002 ± 963

Mean ± SD; *1, median (range); *2, PK analysis was performed for Cycle 1 only; *3, individual values (n = 2); *4, the blood sample from 1 subject had an identification problem, and thus the data were excluded; and *5, n = 23

4.(ii).A.(2).2) Foreign phase II study (5.3.5.1.3, Study ET743-STS-201 [May 2003 to April 2008])

A randomized, open-label, comparative study was conducted in 270 patients (13 patients included in the PK analysis) with unresectable leiomyosarcoma or liposarcoma who had previously been treated with anthracycline and ifosfamide (IFM) chemotherapy, to investigate the efficacy and safety of trabectedin.

In this 21-day cycle study, subjects received an intravenous administration of 20 mg of DEX, and at least 30 minutes later, a 24-hour intravenous infusion of 1.5 mg/m^2 of trabectedin, every 3 weeks; and plasma concentrations were evaluated (see table below).

The results showed that there were no obvious differences in C_{max}, and AUC_{inf} between cycles 1 and 2.

Pharmacokinetic parameters of trabectedin

Cycle	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	$V_{d,ss}$ (L)	MRT (h)
1	7	1.2 ± 0.5	65.0 ± 37.8	138.3 ± 109.2	51.4 ± 25.1	4981 ± 2754	131.0 ± 107.2
2	6	1.4 ± 0.6	63.9 ± 23.1	121.9 ± 38.5	44.3 ± 17.9	4706 ± 1896	116.0 ± 43.4

Mean ± SD; MRT, mean residence time

Based on the PK data obtained from the results of a foreign phase I study (ET-A-002-095) and a foreign phase II study (ET743-STS-201), an analysis was performed using the power model method to assess the dose-proportionality of trabectedin. The applicant considers that C_{max} and AUC in Cycle 1 are dose proportional over the dose range studied, 0.05 to 1.8 mg/m^2.

4.(ii).A.(2).3) Foreign phase I study (5.3.3.3.1, Study ET-A-013-01 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in 8 patients (8 patients included in the PK analysis) with solid cancer to investigate the mass balance and metabolic profile of trabectedin.

In this 21-day cycle study, 1.1 mg of ^{14}C-labelled trabectedin was administered as a 3- or 24-hour intravenous infusion on Day 1 of Cycle 1, and on Day 1 of the subsequent cycles, unlabeled trabectedin was administered at 1.3 mg/m^2 as a 3-hour or at 1.5 mg/m^2 as a 24-hour intravenous infusion. Plasma concentrations and radioactivity levels were evaluated (see table below).

The AUC_{inf} ratio of unchanged trabectedin to total radioactivity was 0.082 (mean value) for the 3-hour infusion, and 0.077 and 0.086 (individual values; n = 2) for the 24-hour infusion, suggesting that the metabolites predominated in plasma compared with unchanged trabectedin.

Up to 240 hours after administration, 5.8% of radiolabelled materials were recovered in urine[*1] (expressed as a percentage of total radioactivity administered, the same applies hereinafter), and up to 408 hours after administration, 57.6% were recovered in feces.[*1] While most of the radiolabelled materials were excreted in feces, only a slight amount of unchanged trabectedin was excreted in feces. Metabolites detected in feces by 408 hours after administration include ET-745 (dehydroxylation), ET-731 (dehydroxylation and demethylation), ETM-217 (deacetylation of ETM259[*2]), ET-729 (*N*-demethylation), ET-759A (carbonyl derivative), and ETM-259.[*2] The excretion of unchanged trabectedin in urine within 240 hours after administration was <1%. Metabolites detected in urine were ET-745, ET-759A, ETM-259,[*2] and ETM-204 (formed by piperazine ring cleavage). No glucuronide conjugates of trabectedin were detected.

Based on the above results, the applicant considered that trabectedin is eliminated primarily by hepatic excretion, and renal excretion is insignificant.

*1, The mean value of the 8 subjects who received a 3-hour or 24-hour intravenous infusion.

*2, The metabolite has a structure which was formed by piperazine ring cleavage in addition to breaking of the bonds between the lactone ring and the hydroxyl group, and between the sulfur atom and the core structure.

Pharmacokinetic parameters of unchanged trabectedin and total radioactivity

Infusion time (h)	Measurement	n	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	$V_{d,ss}$ (L)
3[*1]	Unchanged	6	4.1 ± 1.0	21.6 ± 10.3	28.1 ± 17.3	53.4 ± 5.5	42.7 ± 17.3	1715 ± 466
	Radioactivity	6	9.2 ± 3.0	287 ± 173	440 ± 274	55.1 ± 9.9	3.1 ± 1.8	224 ± 124
24[*2]	Unchanged	2	0.73, 0.61	16.2, 18.3	31.5, 26.6	40.2, 81.8	34.2, 45.2	1345, 3421
	Radioactivity	2	9.69, 4.89	210, 213	454, 345	22.6, 68.9	2.37, 3.48	82.7, 310

*1 Mean ± SD; *2, individual values

4.(ii).A.(2).4) Foreign phase II study (5.3.3.4.3, Study ET-B-010-99 [[redacted] to [redacted]])

A 2-period, 2-treatment crossover study was conducted in 41 patients (38 patients included in the PK analysis) with unresectable STS [see "4.(iii).A. Reference data (2).4) Foreign phase II study"] previously treated with chemotherapy, to investigate the efficacy and safety of trabectedin in combination with DEX or placebo.

In this 21-day cycle study, doses of 1.3, 1.5, or 1.65 mg/m^2 of trabectedin were administered to 8, 25, and 8 subjects, respectively, as a 3-hour intravenous infusion on the first day of each cycle. In addition, 4 mg of DEX or placebo were co-administered to subjects in Groups 1 and 2, respectively, from the day before administration of trabectedin, twice daily for 4 days. Plasma concentrations of trabectedin were evaluated.

The mean ratios [90% confidence interval (CI)] of $t_{1/2}$, CL, and $V_{d,ss}$ of trabectedin (trabectedin plus DEX/trabectedin plus placebo) were 0.79 [0.66, 0.93], 1.28 [1.00, 1.64], and 0.99 [0.75, 1.31], respectively, suggesting that the CL was higher and $t_{1/2}$ was lower in patients receiving trabectedin and DEX than in patients receiving trabectedin and placebo.

The applicant's discussion based on the above study results:

- The results showed that the CL of trabectedin was higher and the $t_{1/2}$ was lower in subjects who received concomitant DEX administration compared to those who did not. This was possibly caused by cytochrome P450 (CYP) 3A induced by DEX, which may have accelerated the metabolism of trabectedin. Given that trabectedin is less likely to inhibit CYP3A in clinical use [see "3.(ii).A.(5).1) *In vitro* enzyme inhibition"], trabectedin is unlikely to significantly affect the PK of DEX (*J Pharmacol Exp Ther* 1996; 277: 105-12), which is metabolized by CYP3A.
- It is considered possible to compare the $t_{1/2}$, CL, and $V_{d,ss}$ of trabectedin between combined administration with DEX and combined administration with placebo by consolidating the PK data for 1.3, 1.5, and 1.65 mg/m^2, for the following reasons: (a) the C_{max} and $AUC_{0\text{-}48h}$ of trabectedin are considered to be dose proportional over the dose range of 0.05 to 1.8 mg/m^2 [see "4.(ii).A.(2).2) Foreign phase II study"]; and (b) the $t_{1/2}$, CL, and $V_{d,ss}$ of trabectedin are not dose-dependent in the above dose range in which dose-proportionality has been observed.

4.(ii).A.(3) Drug interaction studies

4.(ii).A.(3).1) Drug interaction with RFP (5.3.3.4.1, Study ET743-OVC-1002 [January 2011 to [redacted]])

A 2-period, 2-treatment crossover study was conducted in 12 patients (8 patients included in the PK analysis) with solid cancer to investigate the effects of RFP (a CYP3A inducer) on the PK of trabectedin.

This study consisted of two treatment cycles: (a) a cycle of trabectedin monotherapy, and (b) a cycle of trabectedin co-administered with RFP; and each cycle consisted of 21 days. In Cycle (a), subjects received a single dose of 1.3 mg/m^2 of trabectedin as a 3-hour intravenous infusion on Day 1. In Cycle (b), subjects received oral RFP 600 mg once daily on Days 1 to 6, and 1.3 mg/m^2 trabectedin as a 3-hour intravenous infusion on Day 6. There were 7 days between the first and second cycles. Every subject received an intravenous dose of 20 mg of DEX at least 30 minutes prior to the infusion of trabectedin.

The results showed that the geometric mean ratio [90% CI] of the dose-normalized C_{max} and AUC_{inf} of trabectedin (trabectedin plus RFP / trabectedin monotherapy) was 0.78 [0.71, 0.87] and 0.62 [0.51, 0.76],

respectively. The $t_{1/2}$ of trabectedin was 105 hours in the trabectedin monotherapy group and 80.6 hours in the trabectedin plus REP group. The CL was 39.6 L/h in the trabectedin monotherapy group and 59.8 L/h in the trabectedin plus REP group.

The applicant explained that the above study demonstrated that co-administration of trabectedin with the CYP3A inducer decreased the exposure of trabectedin. The applicant will accordingly provide a cautionary statement explaining that co-administration of trabectedin with CYP3A inducers needs to be avoided.

* Dose-normalized PK parameters were used because 2 patients receiving a reduced dose of trabectedin (1.1 mg/m^2) were included in the PK analysis.

4.(ii).A.(3).2) Drug interaction with KCZ (5.3.3.4.2, Study ET743-OVC-1003 [March 2011 to [redacted]])

A 2-period, 2-treatment crossover study was conducted in 12 patients (11 patients included in the PK analysis) with solid cancer to investigate the effects of KCZ (a CYP3A inhibitor) on the PK of trabectedin.

This study consisted of 2 treatment cycles: (a) a cycle of trabectedin monotherapy, and (b) a cycle of trabectedin co-administered with KCZ. Each treatment cycle consisted of 21 days. In Cycle (a), subjects received a single dose of 1.3 mg/m^2 of trabectedin as a 3-hour intravenous infusion on Day 1. In Cycle (b), subjects received 0.2 or 0.58 mg/m^2 of trabectedin (3 and 8 subjects included in the PK analysis, respectively) as a 3-hour intravenous infusion on Day 1, and 6 or 15 oral doses of 200 mg of KCZ, respectively, twice daily, at 12-hour intervals, starting from 12 hours prior to administration of trabectedin. Every subject received an intravenous dose of 20 mg of DEX at least 30 minutes prior to the infusion of trabectedin.

The results showed that the geometric mean ratio [90% CI] of the dose-normalized C_{max} and AUC_{last} of trabectedin (trabectedin plus KCZ / trabectedin monotherapy) was 1.21 [0.77, 1.89] and 1.31 [0.96, 1.80] in the 0.2 mg/m^2 group, and 1.21 [0.96, 1.54] and 1.66 [1.23, 2.24] in the 0.58 mg/m^2 group, respectively. The CL of trabectedin 0.2 mg/m2 was 21.1 L/h in the trabectedin monotherapy group and 16.0 L/h in the trabectedin plus KCZ group. The CL of trabectedin 0.58 mg/m2 was 20.3 L/h in the trabectedin monotherapy group and 12.7 L/h in the trabectedin plus KCZ group.

The applicant explained that the above study demonstrated that co-administration of trabectedin with the CYP3A inhibitor increased the exposure of trabectedin. The applicant will accordingly provide a cautionary statement explaining that co-administration of trabectedin with CYP3A inhibitors needs to be avoided.

4.(ii).A.(4) Effects of renal impairment on the pharmacokinetics of trabectedin

The applicant considered that although no clinical studies had been conducted in patients with renal impairment, renal impairment would not be likely to affect the PK of trabectedin taking the following points into consideration:

- Following intravenous administration of ^{14}C-labelled trabectedin, the urinary excretion rate of radioactivity was 5.8% of the total dose, and unchanged trabectedin represented <1% [see "4.(ii).A.(2).3) Foreign phase I study"].
- Based on the results of population pharmacokinetic (PPK) analysis, creatinine clearance (CrCL) was not identified as a significant covariate on CL of trabectedin [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

4.(ii).A.(5) Analysis of relationship between drug exposure and QT/QTc interval (5.3.4.2.3, Study ET743-OVC-1001 [October 2008 to December 2009])

A single-blind, placebo-controlled study was conducted in 75 patients with solid cancer to investigate the effects of trabectedin on the QT intervals corrected for heart rate using the Fridericia method (QTcF) or Bazett method (QTcB).

In this study, subjects received intravenous DEX 20 mg and, at least 30 minutes later, a 3-hour infusion of 1.3 mg/m^2 of trabectedin (Day 2) or placebo (Day 1).

The upper limits of the 90% CI for all mean placebo-adjusted changes from baseline, ΔΔQTcF and ΔΔQTcB, were <10 msec at all measuring time points. No patients had a QTcF or QTcB value greater than 500 msec. No obvious correlation was observed between concentrations of trabectedin in plasma versus ΔΔQTcF or ΔΔQTcB. C_{max} in this study, 9.2 ± 3.8 ng/mL, was higher than C_{max} in a Japanese phase I study (Study 10045020), 2.1 ± 3.0 ng/mL, following administration of 1.2 mg/m^2 of trabectedin as a 24-hour intravenous infusion [see "4.(ii).A.(1).1) Japanese phase I study"].

The applicant stated, based on the above results, that a 24-hour intravenous infusion of trabectedin 1.2 mg/m^2 was unlikely to cause clinically significant prolongation of QTcF or QTcB.

4.(ii).A.(6) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis was conducted by a non-linear mixed-effect modeling program (NONMEM Ver.V) on the PK data (603 subjects, at 6613 measuring time points) obtained from foreign phase I studies (Studies ET-A-001-95, ET-A-002-95, ET-A-003-95, and ET-A-005-99), and foreign phase II studies (ET-B-005-99, ET-B-008-98, ET-B-010-99, ET743-INT-3, ET743-INT-11, ET-B-001-99, ET-B-002-99, ET-B-013-99, ET-B-009-99, and ET743-STS-201). The PK of trabectedin was described by a 4-compartment model with linear elimination from the central compartment.

The following covariates were assessed for the CL and central compartment volume (Vc) of trabectedin: age, body weight, sex, lean body mass, ideal body weight, body surface area, lactate dehydrogenase

(LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, CrCL, total protein, albumin, Eastern Cooperative Oncology Group performance status, presence/absence of liver metastasis, study, and DEX co-administration. Based on the results, co-administration of DEX was identified as a significant covariate for CL, and it was estimated that CL of trabectedin would be higher by 19% with DEX co-administration than it would be without DEX co-administration. As a significant covariate for Vc, sex was identified, and it was estimated that Vc would be higher by 16% in males than it would be in females. However, given that the degrees of inter-individual variations in CL and Vc of trabectedin, estimated based on the final model (51% and 34%, respectively, as coefficient of variation), the applicant considered that the effects on the CL and Vc of trabectedin caused by DEX co-administration or sex would not be clinically significant.

4.(ii).A.(7) Relationship between drug exposure and efficacy or safety

4.(ii).A.(7).1) Relationship between drug exposure and efficacy

Based on the results of the Japanese phase II study (Study 10045030), the relationship between trabectedin exposure and efficacy was assessed. Data were divided into 2 subgroups by the median value (50.4 ng·h/mL) of $AUC_{0\text{-}t}$ of trabectedin in Cycle 1: the high-exposure subgroup (≥ median of $AUC_{0\text{-}t}$; 19 subjects), and low-exposure subgroup (< median of $AUC_{0\text{-}t}$; 18 subjects). Response and progression-free survival (PFS) assessed by an independent radiology review committee were compared between the subgroups. The results showed that the response rate [95% CI] (%) was 15.8 [3.4, 39.6] and 5.6 [0.1, 27.3] in the high-exposure and low-exposure subgroups, respectively, suggesting that response was higher in the high-exposure subgroup. Progression-free survival (median) [95% CI] (months) was 5.7 [1.9, 11.1] and 7.3 [2.8, 7.5] in the high-exposure and low-exposure subgroups, respectively. The hazard ratio [95% CI] of the PFS in the high-exposure subgroup to the PFS in the low-exposure subgroup calculated by the Cox proportional hazards model was 0.68 [0.27, 1.73], suggesting that no clear differences existed between the subgroups.

4.(ii).A.(7).2) Relationship between drug exposure and safety

The relationship between exposure of trabectedin and bilirubin total increased was investigated given that bilirubin total increased (≥ Grade 2) occurred in clinical studies. Simple and multiple logistic regression analyses were performed on the data from the following studies: foreign phase I studies (Studies ET-A-001-95, ET-A-002-95, ET-A-003-95, and ET-A-005-99), and foreign phase II studies (Studies ET-B-001-99, ET-B-002-99, ET-B-005-98, ET-B-008-98, ET-B-010-99, ET-B-013-99, ET743-INT-3, ET743-INT-11, and ET743-STS-201). The results suggested that C_{max} and AUC of trabectedin in the first cycle might be associated with the incidence of bilirubin total increased (≥ Grade 2).

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

4.(ii).B.(1) Differences in PK between Japanese and non-Japanese populations

Differences in PK of trabectedin between Japanese and foreign populations were investigated on PK data in the first cycle from the following studies: (a) Japanese phase I study (Study 10045020) [see "4.(ii).A.(1).1) Japanese phase I study"]; (b) Japanese phase II study (Study 10045030) [see

"4.(ii).A.(1).2) Japanese phase II study"]; and (c) foreign phase II study (Study ET743-STS-201) [see "4.(ii).A.(2).2) Foreign phase II study"] (see table below).

The results showed that CL and $V_{d,ss}$ of trabectedin tended to be lower in Japanese subjects than in non-Japanese subjects. In addition, C_{max} and AUC_{inf} of trabectedin in Japanese subjects following administration of 1.2 mg/m^2 of trabectedin as a 24-hour intravenous infusion were similar to those in non-Japanese subjects following administration of 1.5 mg/m^2 of trabectedin as a 24-hour intravenous infusion.

PK parameters of trabectedin in Japanese and non-Japanese subjects

	Study	Dose (mg/m^2)	n	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h)	$V_{d,ss}$ (L)
Japanese	10045020	1.2	9	2.1 ± 3.0	74.9 ± 42.7	124 ± 35	31.4 ± 9.5	3380 ± 1050
		1.5	3	2.0 ± 0.7	116, 147[*1]	81.0, 266[*1]	18.2, 24.0[*1]	1940, 5660[*1]
	10045030	1.2	37	1.7 ± 1.7	66.0 ± 24.7[*2]	107 ± 29[*2]	34.3 ± 10.4[*2]	3040 ± 1170[*2]
Non-Japanese	ET743-STS-201	1.5	7	1.2 ± 0.5	65.0 ± 37.8	138.3 ± 109.2	51.4 ± 25.1	4981 ± 2754

Mean ± SD; *1, individual values; *2, n = 33

The applicant's explanation on the reasons for the above differences in PK of trabectedin between Japanese and non-Japanese subjects:
It has been reported that differences in the expression level and activity of CYP3A, one of the major CYP isoforms involved in the metabolism of trabectedin [see "3.(ii).A.(3).1) *In vitro* metabolism"], are not significant between Japanese and non-Japanese populations (*J Pharmacol Exp Ther.* 1994;270:414-23; *Clin Pharmacol Ther.* 2008;84:347-61).

Furthermore, comparisons of $V_{d,ss}$, body surface area, and body weight were performed on data from the Japanese phase I study (Study 10045020), Japanese phase II study (Study 10045030), and foreign phase II study (Study ET743-STS-201). The results showed that the mean $V_{d,ss}$ was significantly higher in non-Japanese subjects (4981 L) than in Japanese subjects (3113 L), while no significant differences were observed for body surface area (1.7 m^2 for both Japanese and non-Japanese subjects), or body weight (64.7 kg for Japanese subjects, and 68.4 kg for non-Japanese subjects).

According to the results of PPK analysis, body weight, lean body mass, ideal body weight, and body surface area were not identified as significant covariates for CL or Vc of trabectedin [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

Based on the above discussions, the reason for the differences in PK of trabectedin between Japanese and non-Japanese populations is not clear at this point.

PMDA's view:

Given the large inter-individual variations in trabectedin PK and the small number of Japanese and non-Japanese patients included in the trabectedin PK analyses, it is difficult to assess differences in PK of trabectedin between Japanese and non-Japanese populations based on study results available at this point. Therefore, it is necessary to collect data that allow evaluation of differences in PK of trabectedin between Japanese and non-Japanese populations, and when new findings become available, the information should be distributed to healthcare professionals in an appropriate manner.

4.(ii).B.(2) Effects of decreased hepatic function on the PK of trabectedin

While results of clinical studies which have analyzed trabectedin PK in patients with hepatic impairment are not available at this point, the applicant explained the effects of decreased hepatic function on the PK of trabectedin as follows. Currently, a foreign phase I/II study (Study ET743-OVC-1004) is underway examining the PK of trabectedin in patients with hepatic impairment.

Given that trabectedin is primarily eliminated by hepatic metabolism [see "4.(ii).A.(2).3) Foreign phase I study"], decreased hepatic function can lower the CL of trabectedin, leading to its delayed elimination. Therefore, when trabectedin is administered to patients with hepatic impairment, careful administration is required, and dose reduction needs to be considered. It is necessary to advise caution with regard to this point in the "Precautions for dosage and administration" section.

PMDA's view:

Results of clinical studies which aim to investigate the effects of hepatic impairment on trabectedin PK, and the efficacy and safety of trabectedin in patients with hepatic impairment following administration of a reduced dose of trabectedin are not available at this point. Therefore, it is not appropriate to include a caution statement that doses of trabectedin should be reduced in patients with hepatic impairment in the "Precautions for dosage and administration" section of the package insert. However, given that trabectedin is primarily eliminated by hepatic metabolism [see "4.(ii).A.(2).3) Foreign phase I study"], and that the efficacy and safety of trabectedin in patients with hepatic impairment are unknown because such patients were excluded from the Japanese clinical studies (Studies 10045020, 10045030, and 10045040), caution should be included in the package insert and other relevant materials to ensure that careful administration is required when administering trabectedin to patients with hepatic impairment.

When the results of Study ET743-OVC-1004 become available, the information should be distributed to healthcare professionals in an appropriate manner, and if necessary, caution should be advised with regard to administration to patients with hepatic impairment.

4.(iii) Summary of clinical efficacy and safety

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

The applicant submitted efficacy and safety evaluation data (the results from 3 Japanese studies [1 phase I study and 2 phase II studies]) and reference data (the results from 16 foreign studies [3 phase I, 3 phase I/II, 9 phase II, and 1 phase III studies]).

List of clinical studies on efficacy and safety

Data	Location	Study Identifier	Phase	Population	Subjects enrolled	Summary of dosage regimen	Major endpoints
Evaluation data	Japan	10045020	I	Patients with STS previously treated with chemotherapy	15	Doses of 0.9, 1.2, or 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Safety PK
		10045030	II	Patients previously treated with chemotherapy for STS of histological subtypes reported to carry chromosomal translocations	(1)39 (2)37	(1) Doses of 1.2 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks. (2) BSC	Efficacy Safety PK
		10045040	II	Patients in the BSC group of Study 10045030	31	Doses of 1.2 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Safety Efficacy
Reference data	Foreign	ET-A-002-95	I	Patients with solid cancer	52	Doses of 0.05, 0.1, 0.2, 0.4, 0.6, 0.9, 1.2, 1.5, or 1.8 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Safety PK
		ET-A-006-00	I	Patients with solid cancer and hepatic impairment	33	Doses of 0.75, 0.9, or 1.1 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion.	Safety PK
		ET-A-013-01	I	Patients with solid cancer	8	Doses of 1.1, 1.3, or 1.5 mg/m^2 of trabectedin were administered as a 3-hour or 24-hour intravenous infusion every 3 weeks.	Safety PK
		ET743-OVC-1001	I/II	Patients with solid cancer	75	Single-blind part, Placebo was administered on Day 1 as a 3-hour intravenous infusion; a dose of 1.3 mg/m^2 of trabectedin was administered as a 3-hour intravenous infusion on Day 2. Open-label extension part, Doses of 1.2 or 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 17-49 days.	Safety PK
		ET743-OVC-1002	I/II	Patients with solid cancer	(1) 6 (2) 6	(1) On Days 1-6, oral doses of 600 mg of RFP were administered once daily, and doses of 1.3 mg/m^2 of trabectedin were administered on Days 6 and 34 as a 3-hour intravenous infusion. (2) On Days 1 and 29, doses of 1.3 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion; on Days 24-29, oral doses of 600 mg of RFP were administered once daily.	Safety PK

Data	Location	Study Identifier	Phase	Population	Subjects enrolled	Summary of dosage regimen	Major endpoints
		ET743-OVC-1003	I/II	Patients with solid cancer	(1) 8 (2) 4	(1) On Days 1 and 22, doses of 0.2 and 1.3 mg/m^2 of trabectedin, respectively, were administered as a 3-hour intravenous infusion, and on Days 1-3, oral doses of 200 mg of KCZ were administered twice daily; or on Days 1 and 22, doses of 0.58 and 1.3 mg/m^2, respectively, were administered as a 3-hour intravenous infusion, and on Days 1-8, oral doses of 200 mg of KCZ were administered twice daily. (2) On Days 1 and 22, doses of 1.3 and 0.58 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion, and on Days 22-29, oral doses of 200 mg of KCZ were administered twice daily.	Safety PK
		ET743-STS-201	II	Patients previously treated with chemotherapy for leiomyosarcoma or liposarcoma	(1) 134 (2) 136	(1) Doses of 0.58 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion every 4 weeks. (2) Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-005-98	II	Patients with STS previously treated with chemotherapy	104	Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-008-98	II	Patients with STS previously treated with chemotherapy	54	Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-010-99	II	Patients with STS previously treated with chemotherapy	41	Doses of 1.3, 1.5, or 1.65 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-016-99	II	Chemotherapy-naïve patients with STS	36	Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-017-99	II	Patients with STS previously treated with chemotherapy	37	Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-022-00	II	Patients with STS previously treated with chemotherapy	69	Doses of 1.5 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-023-00	II	Patients previously treated with chemotherapy for STS or osteosarcoma	75	Doses of 1.5 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-B-028-06	II	Chemotherapy-naïve patients with MRCL	29	Doses of 1.5 mg/m^2 of trabectedin were administered as a 3-hour intravenous infusion every 3 weeks.	Efficacy Safety
		ET-C-002-07	III	Chemotherapy-naïve patients with STS of histological subtypes reported to carry chromosomal translocations	(1) 61 (2) 60	(1) Doses of 1.5 mg/m^2 of trabectedin were administered as a 24-hour intravenous infusion every 3 weeks. (2) Monotherapy with DOX 75 mg/m^2, or DOX 60 mg/m^2 + IFM 6-9 g/ m^2 intravenously administered every 3 weeks.	Efficacy Safety

STS, soft tissue sarcoma; PK, pharmacokinetics; BSC, best supportive care; MRCL, myxoid/round cell liposarcoma; DOX, doxorubicin hydrochloride; KCZ, ketoconazole; IFM, ifosfamide; and RFP, rifampicin

The studies are summarized in the following sections.

Main adverse events observed in each study except for death are described in the "4.(iv) Adverse events and other relevant findings observed in clinical studies" section, and study results on PK are in the sections, "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

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

4.(iii).A.(1).1) Japanese phase I study (5.3.3.2.1, Study 10045020 [September 2010 to July 2013])

An open-label, uncontrolled study was conducted at 3 study sites in Japan in patients with unresectable STS (maximum target sample size, 36 subjects) previously treated with chemotherapy, to investigate the recommended dose, safety, and PK of trabectedin.

In this study, patients received a 24-hour intravenous infusion of 0.9, 1.2, or 1.5 mg/m^2 of trabectedin every 3 weeks.

All the 15 subjects enrolled in the study received trabectedin, and were included in the safety analysis population.

Dose-limiting toxicity (DLT) occurred in 2 of 3 subjects (blood creatine phosphokinase [CPK] increased/decreased appetite in 1 subject, and platelet count decreased in 1 subject) in the 1.5 mg/m^2 group. The MTD and recommended dose of trabectedin were determined to be 1.5 mg/m^2 and 1.2 mg/m^2, respectively.

No deaths occurred during the treatment period or within 28 days after the completion of treatment with trabectedin.

4.(iii).A.(1).2) Japanese phase II study (5.3.5.1.1, Study 10045030 [ongoing since July 2012, data cut-off on February 8, 2014])

An open-label, randomized, comparative study was conducted at 12 study sites in Japan. The study enrolled chemotherapy-naïve patients* with unresectable STS of histological subtypes reported to carry chromosomal translocations (maximum target sample size, 74 subjects), to assess the efficacy and safety of trabectedin compared with best supportive care (BSC).

* Patients meeting the following criteria were eligible for enrollment:

(1) For patients with the following histological subtypes of STS: myxoid/round cell liposarcoma, synovial sarcoma, and extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor, patients who had been treated with chemotherapy including anthracycline, to which STS was resistant to, or to which the patient was intolerant.

(2) For patients with histological subtypes of STS other than above (alveolar rhabdomyosarcoma, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, alveolar soft part sarcoma, clear cell sarcoma,

angiomatoid fibrous histiocytoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, giant cell fibroblastoma, and endometrial stromal sarcoma), patients who had been treated with standard chemotherapy at the medical institution, to which STS was resistant to, or to which the patient was intolerant.

In this study, subjects received a 24-hour intravenous infusion of 1.2 mg/m^2 of trabectedin every 3 weeks, and continued treatment until they experienced disease progression or met the discontinuation criteria.

In total, 76 subjects were enrolled in the study (39 subjects in the trabectedin group, and 37 subjects in the BSC group). Of the 76 subjects, 3 were excluded from efficacy analysis because they had STS histological subtypes not listed in the inclusion criteria, as diagnosed by the central histopathological review (2 subjects in the trabectedin group, and 1 subject in the BSC group). As a result, the remaining 73 subjects (37 subjects in the trabectedin group, and 36 subjects in the BSC group) were included in the full analysis set (FAS) for the efficacy analysis. Among the 76 subjects enrolled in the study, 3 subjects did not complete the first cycle period by the data cut-off date and thus the safety evaluation could not be performed. These 3 subjects were excluded and the remaining 73 subjects (36 subjects in the trabectedin group, and 37 subjects in the BSC group) were included in the safety analysis population.

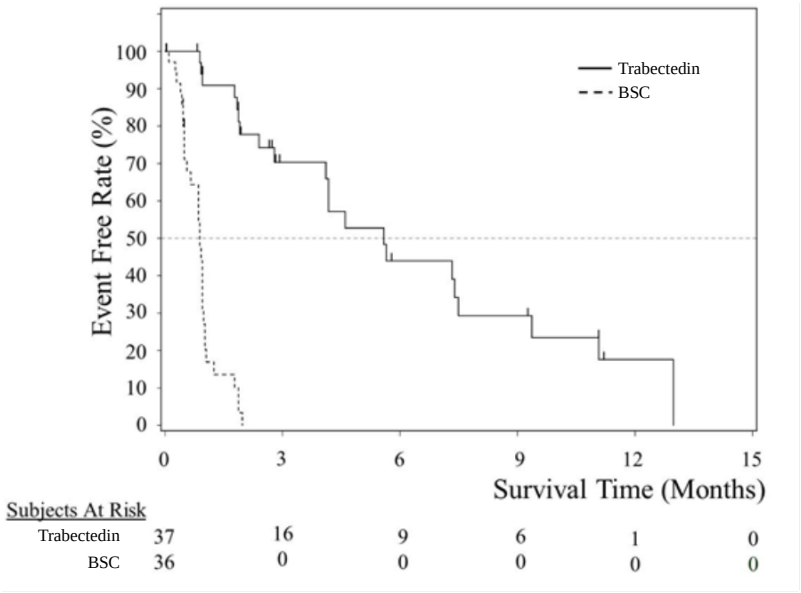
The primary endpoint for the study was PFS by an independent radiology review committee (central review).

The PFS results for this study and Kaplan-Meier plots are shown in the table and figure below, respectively.

PFS analysis results (FAS, central review, data cut-off on February 8, 2014)

	Trabectedin	BSC
Number of subjects	37	36
Number of deaths or exacerbations (%)	21 (56.8)	31 (86.1)
Median [90% CI] (months)	5.6 [4.2, 7.5]	0.9 [0.9, 1.0]
Hazard ratio [90% CI][*1]	0.07 [0.03, 0.14]	
P-value (one-sided)[*2]	<0.0001	

*1, Cox regression adjusted for the stratification factor, histological subtype (“histological subtype of myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, or extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor,” “other histological subtypes”); *2, a stratified log rank test using histological subtype (“histological subtype of myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, or extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor,” “other histological subtypes”) as the stratification factor, one-sided significance level, 0.05.



Kaplan-Meier plots of PFS (FAS, central review, data cut-off on February 8, 2014)

No deaths occurred in the trabectedin group during the treatment period or within 28 days after the completion of treatment with trabectedin. Deaths (due to disease progression) occurred in 2 of 37 subjects (5.4%) in the BSC group within 30 days of the enrollment.

4.(iii).A.(1).3) Japanese phase II study (5.3.5.2.1, Study 10045040 [ongoing since August 2012, data cut-off on February 8, 2014])

An open-label, uncontrolled study was conducted at 12 study sites in Japan to assess the safety and other aspects of trabectedin in patients who experienced disease progression after being randomized to the BSC group in Study 10045030 (maximum target sample size, 37 subjects).

In this study, subjects received 1.2 mg/m^2 of trabectedin as a 24-hour intravenous infusion every 3 weeks. Treatment continued until disease progression occurred or the study discontinuation criteria were met.

Among the 31 subjects enrolled in the study, 30 subjects received trabectedin. Of the 30 subjects, 2 were excluded from safety evaluation because they did not complete the first cycle period by the data cut-off date. The remaining 28 subjects were included in the safety analysis population.

One of the 28 subjects (3.6%) died from disease progression during the treatment period or within 28 days after the completion of treatment with trabectedin, and a causal relationship to trabectedin was ruled out.

Reference data

4.(iii).A.(1) Clinical pharmacology studies

The applicant submitted the results of the following 6 clinical pharmacology studies in patients with solid cancer. Deaths occurred in 16 subjects (7 subjects in Study ET-A-002-95, 1 subject in Study ET-

A-006-00, 7 subjects in Study ET743-OVC-1001, and 1 subject in Study ET743-OVC-1003) during the treatment period or within 30 days after the last dose of trabectedin. The causes of deaths were disease progression in 4 subjects, sepsis in 2 subjects, euthanasia, upper gastrointestinal haemorrhage/anaemia, oropharyngeal cancer, completed suicide, osteosarcoma, colon cancer, vomiting/asthenia, hepatic failure/renal failure/respiratory failure, disseminated intravascular coagulation, and headache/asthenia/nausea/vomiting in 1 subject each. A causal relationship to trabectedin could not be ruled out in hepatic failure/renal failure/respiratory failure (1subject) and sepsis (1subject).

4.(iii).A.(1).1) Foreign phase I study (5.3.3.2.2, Study ET-A-002-95 [May 1996 to June 1999])

4.(iii).A.(1).2) Foreign phase I study (5.3.3.3.2, Study ET-A-006-00 [August 2001 to February 2006])

4.(iii).A.(1).3) Foreign phase I study (5.3.3.3.1, Study ET-A-013-01 [to])

4.(iii).A.(1).4) Foreign phase I/II study (5.3.4.2.3, Study ET743-OVC-1001 [October 2008 to December 2009])

4.(iii).A.(1).5) Foreign phase I/II study (5.3.3.4.1, Study ET743-OVC-1002 [January 2011 to])

4.(iii).A.(1).6) Foreign phase I/II study (5.3.3.4.2, Study ET743-OVC-1003 [March 2011 to])

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

4.(iii).A.(2).1) Foreign phase II study (5.3.5.1.3, Study ET743-STS-201 [May 2003 to April 2008])

An open-label, dose-comparison study was conducted in patients with unresectable leiomyosarcoma or liposarcoma who had received chemotherapy with anthracycline and IFM (target sample size, 260 subjects) at 47 foreign study sites to investigate the efficacy and safety of trabectedin.

In this study, trabectedin was administered according to 2 different schedules: a 3-hour intravenous infusion of 0.58 mg/m^2 of trabectedin on Days 1, 8, and 15 of each 4-week cycle (the QW-3h group); or a 24-hour intravenous infusion of 1.5 mg/m^2 of trabectedin on Day 1 of each 3-week cycle (the Q3W-24h group).

Among the 270 subjects enrolled in the study (134 subjects in the QW-3h group and 136 subjects in the Q3W-24h group), 10 subjects (4 subjects in the QW-3h group and 6 subjects in the Q3W-24h group) who did not receive trabectedin were excluded, and the remaining 260 subjects (130 subjects each in the QW-3h group and Q3W-24h group) were included in the efficacy analysis population, which was also used for the safety analysis.

The median value [95% CI] (months) of time to progression (TTP) assessed by the central review, the primary endpoint for the study, was 2.3 [2.0, 3.5] in the QW-3h group, and 3.7 [2.1, 5.4] in the Q3W-24h group.

During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 7 of 130 subjects (5.4%) in the QW-3h group, and 7 of 130 subjects (5.4%) in the Q3W-24h group. The causes of deaths were recall phenomenon/radiation pneumonitis/ leiomyosarcoma metastatic, hydronephrosis, cerebrovascular disorder, disseminated intravascular coagulation/multi-organ failure, pulmonary embolism, sepsis, and cardio-respiratory arrest/dyspnoea/depressed level of consciousness/hypotension in 1 subject each in the QW-3h group; non-cardiogenic pulmonary oedema, shock/multi-organ failure, pneumonia/disease progression/pulmonary oedema, acute myeloid leukaemia, septic shock, renal failure acute, and sarcoma/respiratory failure in 1 subject each in the Q3W-24h group. Among these cases, a causal relationship to trabectedin could not be ruled out for the following: recall phenomenon/radiation pneumonitis, disseminated intravascular coagulation/multi-organ failure, and sepsis in 1 subject each in the QW-3h group; and non-cardiogenic pulmonary oedema, pneumonia/disease progression/pulmonary oedema, acute myeloid leukaemia, and renal failure acute in 1 subject each in the Q3W-24h group.

4.(iii).A.(2).2) Foreign phase II study (5.3.5.2.2, Study ET-B-005-98 [March 1999 to [redacted]])

An open-label, uncontrolled study was conducted in patients with unresectable STS* previously treated with chemotherapy (target sample size, 44 subjects) at 8 foreign study sites to investigate the efficacy and safety of trabectedin.

*Patients with STS of one of the following histological subtypes were included in the study: malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, malignant paraganglioma, fibrosarcoma, leiomyosarcoma, angiosarcoma including haemangiopericytoma, neurogenic sarcoma, unclassified sarcoma, or sarcoma of other histological subtypes including mixed mesodermal tumor of the uterus.

Among the 104 subjects enrolled in the study, 99 subjects who received trabectedin were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 13 of 99 subjects (13.1%). Six of the 13 subjects died from disease progression. Other causes of deaths were generalized oedema, haemorrhage/pulmonary oedema, cerebral haemorrhage, neutropenic sepsis, renal failure/febrile neutropenia, renal failure/neutropenia/sepsis, and catheter-related infection/sepsis in 1 subject each. Among these events, a causal relationship to trabectedin could not be ruled out for the following: generalized oedema, haemorrhage/pulmonary oedema, neutropenic sepsis, renal failure/febrile neutropenia, and renal failure/neutropenia/sepsis in 1 subject each.

4.(iii).A.(2).3) Foreign phase II study (5.3.5.2.3, Study ET-B-008-98 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in patients with unresectable STS* previously treated with chemotherapy (maximum target sample size, 54 subjects) at 4 foreign study sites, to investigate the efficacy and safety of trabectedin.

*Patients with STS of one of the following histological subtypes were included in the study: fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, Ewing's sarcoma in soft tissues,

synovial sarcoma, angiosarcoma including haemangiopericytoma, Schwannoma malignant, chondrosarcoma, or unclassified sarcoma.

All the 54 subjects enrolled in the study received trabectedin and were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 4 of 54 subjects (7.4%). The causes of death for 2 subjects were attributed to disease progression. Other causes of deaths were hepatic cirrhosis, and rhabdomyolysis/renal failure acute/febrile neutropenia/thrombocytopenia in 1 subject each; a causal relationship to trabectedin could not be ruled out for any of these events.

4.(iii).A.(2).4) Foreign phase II study (5.3.3.4.3, Study ET-B-010-99 [to])

A double-blind, randomized study was conducted in patients with unresectable STS* previously treated with chemotherapy (target sample size, 64 subjects) at 10 foreign study sites to investigate the efficacy and safety of trabectedin.

*Patients with STS of one of the following histological subtypes were included in the study: fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, synovial sarcoma, angiosarcoma including haemangiopericytoma, neurogenic sarcoma, malignant paraganglioma, other sarcoma, or unclassified histological subtype sarcoma.

All the 41 subjects enrolled in the study received trabectedin, and were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 7 of 41 subjects (17.1%). Two of the 7 subjects died from disease progression. Other causes of deaths were pneumonia bacterial/disease progression, septic shock/multi-organ failure, cardiac failure/renal failure/rhabdomyolysis, cardiac failure, and ventricular fibrillation/acute pulmonary oedema in 1 subject each. Among these events, a causal relationship to trabectedin could not be ruled out for the following: septic shock/multi-organ failure, cardiac failure/renal failure/rhabdomyolysis, cardiac failure, and ventricular fibrillation/acute pulmonary oedema in 1 subject each.

4.(iii).A.(2).5) Foreign phase II study (5.3.5.2.4, Study ET-B-016-99 [to])

An open-label, uncontrolled study was conducted in chemotherapy-naïve patients with unresectable STS* (target sample size, 35 subjects) at 3 foreign study sites, to investigate the efficacy and safety of trabectedin.

*Patients with STS of one of the following histological subtypes were included in the study: fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma (pleomorphic), synovial sarcoma, angiosarcoma including haemangiopericytoma, Schwannoma malignant, chondrosarcoma, or unclassified histological subtype sarcoma.

All the 36 subjects enrolled in the study received trabectedin, and were included in the safety analysis population. No deaths occurred during the treatment period or within 30 days of the completion of treatment with trabectedin.

4.(iii).A.(2).6) Foreign phase II study (5.3.5.2.5, Study ET-B-017-99 [September 1999 to [redacted]])

An open-label, uncontrolled study was conducted in patients with unresectable STS* previously treated with chemotherapy (maximum target sample size, 35 subjects) at 3 foreign study sites to investigate the efficacy and safety of trabectedin.

*Patients with STS of one of the following histological subtypes were included in the study: fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, Ewing's sarcoma in soft tissues, synovial sarcoma, angiosarcoma including haemangiopericytoma, Schwannoma malignant, chondrosarcoma, or unclassified histological subtype sarcoma.

Among the 37 subjects enrolled in the study, 36 subjects who received trabectedin were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 2 of 36 subjects (5.6%). The deaths were due to disease progression, and a causal relationship to trabectedin was ruled out for all of these patients.

4.(iii).A.(2).7) Foreign phase II study (5.3.5.2.6, Study ET-B-022-00 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in patients previously treated with chemotherapy for unresectable STS* (target sample size, 56 subjects) at 3 foreign study sites to investigate the efficacy and safety of trabectedin.

*The study excluded patients with STS of the following histological subtypes: gastrointestinal stromal tumour, human immunodeficiency virus-associated Kaposi’s sarcoma, mesothelioma malignant, or chondrosarcoma. Patients with STS of other subtypes were included.

Among the 69 subjects enrolled in the study, 68 subjects who received trabectedin were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, deaths occurred in 2 of 68 subjects (2.9%). The causes of deaths were pulmonary embolism, and respiratory failure in 1 subject each, and a causal relationship to trabectedin was ruled out for both patients.

4.(iii).A.(2).8) Foreign phase II study (5.3.5.2.7, Study ET-B-023-00 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in patients previously treated with chemotherapy for unresectable STS or osteosarcoma (target sample size, 71 subjects) at 7 foreign study sites to investigate the efficacy and safety of trabectedin.

All the 75 subjects enrolled in the study received trabectedin, and were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with

trabectedin, deaths occurred in 3 of 75 subjects (4.0%). The causes for deaths were osteosarcoma metastatic, pulmonary oedema, and febrile neutropenia in 1 subject each. Among the death cases, a causal relationship to trabectedin could not be ruled out for the patient with febrile neutropenia.

4.(iii).A.(2).9) Foreign phase II study (5.3.5.2.8, Study ET-B-028-06 [April 2007 to January 2010])

An open-label, uncontrolled study was conducted in patients with myxoid/round cell liposarcoma (target sample size, 31 subjects) at 8 foreign study sites to investigate the efficacy and safety of neoadjuvant trabectedin.

All the 29 subjects enrolled in the study received trabectedin, and were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment with trabectedin, 1 death occurred (in 1 of 29 subjects; 3.4%). The cause of death was renal insufficiency and rhabdomyolysis, and a causal relationship to trabectedin could not be ruled out for this patient.

4.(iii).A.(2).10) Foreign phase III study (5.3.5.1.2, Study ET-C-002-07 [November 2008 to August 2012])

An open-label, controlled study was conducted in chemotherapy-naïve patients with unresectable STS* of histological subtypes reported to carry chromosomal translocations (target sample size, 80 subjects) at 22 foreign study sites, to assess the efficacy and safety of trabectedin monotherapy (the trabectedin group) in comparison to chemotherapy including doxorubicin hydrochloride (DOX) (the DOX group) [see "4.(iii).B.(4) Clinical positioning and indications"].

> * Patients with one of the following histological subtypes of STS were included in the study: myxoid/round cell liposarcoma, synovial sarcoma, alveolar soft part sarcoma, low grade fibromyxoid sarcoma, clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small round cell tumor, myxoid chondrosarcoma, or low grade endometrial stromal sarcoma.

Among the 121 subjects (61 subjects in the trabectedin group and 60 subjects in the DOX group) enrolled in the study, 118 subjects who received the study drug (61 subjects in the trabectedin group and 57 subjects in the DOX group) were included in the safety analysis population. During the treatment period or within 30 days of the completion of treatment, deaths occurred in 5 of 61 subjects (8.2%) in the trabectedin group, and 1 of 57 subjects (1.8%) in the DOX group. Three of the 5 subjects in the trabectedin group died from disease progression. Other causes of deaths were rhabdomyolysis and duodenal perforation in 1 subject each in the trabectedin group; pneumonia in 1 subject in the DOX group. A causal relationship to the study drug could not be ruled out for rhabdomyolysis (the trabectedin group) and pneumonia (the DOX group).

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

4.(iii).B.(1) Premise for review

PMDA considered that, among the data submitted, the most important study was the Japanese phase II study (Study 10045030), which evaluated the efficacy and safety of trabectedin in patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations. Therefore, PMDA decided to review the application data focusing on this study.

In addition, another ongoing Japanese phase II study (Study 10045050) aims to assess the safety of trabectedin in patients previously treated with chemotherapy for locally advanced or recurrent STS of histological subtypes reported to carry chromosomal translocations. PMDA decided to also review the data obtained so far from Study 10045050. A review summary is presented below.

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

Based on the following review, PMDA concluded that trabectedin has been shown to have a certain degree of efficacy in the treatment of patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations, the target population of Study 10045030.

4.(iii).B.(2).1) Selection of comparator

The applicant justified the selection of best supportive care (BSC) as the comparator in Study 10045030 on the grounds that, at the time when this study was planned, there was no established standard treatment for patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations.

PMDA accepted the applicant's rationale.

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

PFS was used as the primary endpoint in Study 10045030. PMDA asked the applicant to explain the appropriateness of PFS as the primary endpoint.

The applicant's explanation:

While the mainstay of treatment for STS is curative resection, patients with unresectable STS are treated with palliative chemotherapy in the absence of treatment options that can cure their condition (*A Practical Guide to Treatment of Soft Tissue Tumors*, Nakayama Shoten, 2011; *Latest Orthopedics vol. 20, Bone and Soft Tissue Tumors and Related Conditions*, Nakayama Shoten, 2007). In light of this background, prolongation of PFS in these patients is considered to be clinically meaningful because suppression of tumor growth is expected to stabilize symptoms such as tumor pain and dyspnea due to lung metastasis.

Therefore, PFS was appropriate as the primary endpoint in Study 10045030.

PMDA's view:

Given that improving survival is the therapeutic objective for patients with unresectable STS, the primary endpoint for Study 10045030 should have been overall survival (OS). However, the applicant's explanation is reasonable in that prolongation of PFS has certain clinical benefits for these patients, such as delaying the onset of events resulting from tumor progression. Therefore, it is acceptable to evaluate the efficacy of trabectedin based primarily on PFS results if OS results (a secondary endpoint in this study) are taken into consideration.

4.(iii).B.(2).3) Results of efficacy evaluation

Study 10045030 demonstrated the superiority of trabectedin over BSC in PFS assessed by the central review, the primary endpoint [see "4.(iii).A. Evaluation data (1).2) Japanese phase II study"].

The table below shows the results of a sensitivity analysis of investigator-assessed PFS.

Results of PFS analysis (FAS, assessed by investigators, data cut-off on February 8, 2014)

	Trabectedin	BSC
Number of subjects	37	36
Number of deaths or exacerbations (%)	25 (67.6)	33 (91.7)
Median [90% CI] (months)	4.2 [1.9, 5.7]	0.9 [0.5, 1.0]
Hazard ratio [90% CI][*1]	0.13 [0.07, 0.24]	
P-value (one-sided)[*2]	<0.0001	

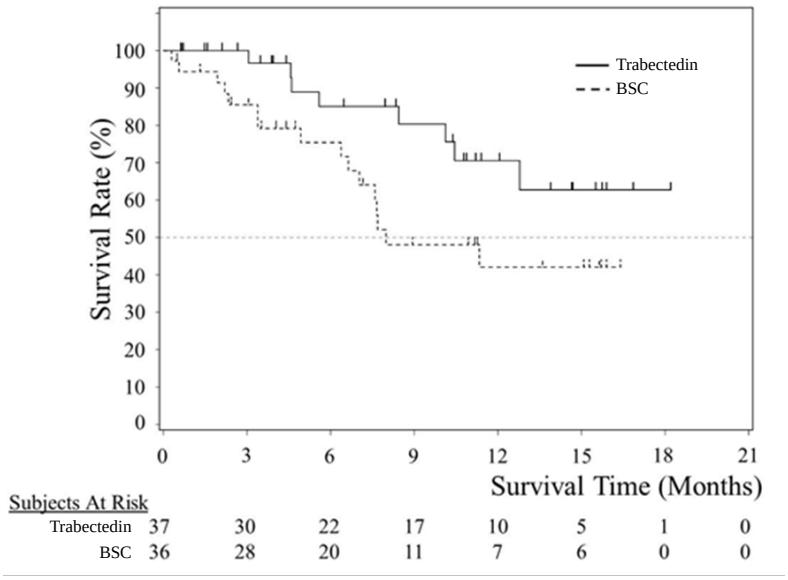
*1, Cox regression adjusted for the stratification factor, histological subtype ("histological subtype of myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, or extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor," "other histological subtypes"); *2, a stratified log rank test stratified with histological subtype ("histological subtype of myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, or extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor," "other histological subtypes")

The results and Kaplan-Meier plots of OS, a secondary endpoint of the study, are shown in the table and figure below. At the time of OS analysis, 30 of the 36 subjects (83.3%) in the BSC group in Study 10045030 had been enrolled in Study 10045040, and 29 of the enrolled 36 subjects (80.6%) had received trabectedin.

Results of OS analysis (FAS, data cut-off on February 8, 2014)

	Trabectedin	BSC
Number of subjects	37	36
Number of deaths (%)	8 (21.6)	16 (44.4)
Median [95% CI] (months)	NE [12.8, NE]	8.0 [7.0, NE]
Hazard ratio [95% CI][*1]	0.42 [0.18, 0.98]	
P-value (one-sided)[*2]	0.019	

NE, not estimable; *1, unadjusted Cox regression; *2, unstratified log-rank test



Kaplan-Meier plots for OS (FAS, data cut-off on February 8, 2014)

PMDA's view:

Study 10045030 was planned and conducted as an exploratory study on the efficacy of trabectedin, it is therefore difficult to evaluate the efficacy of trabectedin based solely on the results of Study 10045030. Nevertheless, given that Study 10045030 demonstrated the superiority of trabectedin over BSC in PFS assessed by the central review, the primary endpoint [see "4.(iii).A. Evaluation data (1).2) Japanese phase II study"], and also on the basis of the discussions summarized below, PMDA concluded that trabectedin has been shown to have a certain degree of efficacy in the treatment of patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations.

- Trabectedin was shown to be superior to BSC in PFS assessed by investigators as well as PFS assessed by the central review, the primary endpoint. The degree of efficacy in PFS was clinically meaningful.
- Trabectedin was not shown to be inferior to BSC in OS, a secondary endpoint.

4.(iii).B.(2).4) Efficacy against each histological subtype

PMDA asked the applicant to explain the efficacy against each histological subtype evaluated in Study 10045030.

The applicant's explanation:

The efficacy in patients previously treated with chemotherapy for unresectable STS of histological types reported to carry chromosomal translocations was reviewed for each histological tumor subtype by classifying the subtypes into Category (a) or (b).

(a) Histological subtypes included in both the trabectedin and BSC groups

In Study 10045030, both the trabectedin and BSC groups included patients with myxoid/round cell liposarcoma, alveolar rhabdomyosarcoma, synovial sarcoma, alveolar soft part sarcoma, clear cell sarcoma, mesenchymal chondrosarcoma, and extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor. The PFS assessed by the central review for each histological subtype is shown in the table below. In the subgroup analyses of all histological subtypes, PFS tended to be longer in the trabectedin group than in the BSC group. Trabectedin is thus expected to be effective for the above histological subtypes of STS.

Results of PFS analysis by histological subtype (central review, FAS, data cut-off on February 8, 2014)

Histological subtype (assessed at study site)	Trabectedin		BSC		Hazard ratio [95% CI]*
	Number of subjects	Median [95% CI] (months)	Number of subjects	Median [95% CI] (months)	
Myxoid/ round cell liposarcoma	14	7.3 [5.6, 11.1]	10	0.9 [0.5, 1.0]	0.03 [<0.01, 0.22]
Alveolar rhabdomyosarcoma	2	NE [1.8, NE]	3	0.6 [0.1, 0.9]	<0.01 [<0.01, NE]
Synovial sarcoma	7	3.5 [1.8, 4.6]	11	0.9 [0.7, 1.1]	0.14 [0.03, 0.68]
Alveolar soft part sarcoma	3	4.1 [1.0, 4.1]	2	1.6 [1.2, 1.9]	0.53 [0.05, 6.16]
Clear cell sarcoma	1	2.8 [NE, NE]	4	0.7 [0.3, 1.8]	<0.01 [<0.01, NE]
Mesenchymal chondrosarcoma	3	NE [NE, NE]	3	1.0 [0.3, 1.0]	<0.01 [<0.01, NE]
Extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor	3	2.5 [0.9, 4.2]	2	1.0 [0.9, 1.0]	0.62 [0.05, 7.00]

NE, not estimable; *, unstratified Cox regression

(b) Histological subtypes included only in the trabectedin group but not in the BSC group, or histological subtypes not treated with trabectedin

In Study 10045030, patients with dermatofibrosarcoma protuberans, angiomatoid fibrous histiocytoma, and extraskeletal myxoid chondrosarcoma were confined to the trabectedin group and none were in the BSC group; trabectedin was not administered to patients with low-grade fibromyxoid sarcoma, giant cell fibroblastoma, endometrial stromal sarcoma, or desmoplastic small round cell tumor. For these histological subtypes, therefore, efficacy cannot be compared between the trabectedin and BSC groups. However, the results of the analyses by histological subtype in Category (a) suggest that trabectedin can be expected to be effective for STS of histological subtypes reported to carry chromosomal translocations and were included in both the trabectedin and BSC groups. Given this, it is considered that trabectedin would be effective for those histological subtypes included only in the trabectedin group but not in the BSC group, and subtypes for which trabectedin was not administered.

PMDA's view:

The applicant's explanation concerning Category (a) is acceptable; however, it is difficult to evaluate the efficacy of trabectedin against histological subtypes of Category (b) based solely on the results of Study 10045030, and the applicant's explanation does not go beyond speculation [see "4.(iii).B.(4) Clinical positioning and indications"].

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

Based on the following review, PMDA concluded that close attention is required for the following adverse events: bone marrow depression, febrile neutropenia, hepatic dysfunction, gastrointestinal disorder, rhabdomyolysis, injection site reaction, hypersensitivity, secondary malignancy, and pancreatitis. These adverse events should be monitored closely when administering trabectedin.

PMDA concluded that the tolerability of trabectedin is acceptable provided that possible adverse events are closely monitored and controlled, and appropriate response measures are taken including treatment interruption, dose reduction, or treatment discontinuation, by a physician with sufficient knowledge and experience in chemotherapy. However, safety information available at this point is not sufficient; therefore, data need to be continuously collected after trabectedin is released to the market [see "4.(iii).B.(6) Post-marketing investigations"].

4.(iii).B.(3).1) Safety profile and differences between Japanese and non-Japanese patients

The applicant provided the following explanation on the safety profiles of trabectedin in patients with STS previously treated with chemotherapy on the basis of safety data obtained in Study 10045030. The table below summarizes the safety profiles in the trabectedin and BSC groups for Study 10045030.

Summary of safety (Study 10045030)

	Number of subjects (%)	
	Trabectedin 36 subjects	BSC 37 subjects
Adverse events total	36 (100)	24 (64.9)
≥ Grade 3 adverse events	34 (94.4)	5 (13.5)
Serious adverse events	12 (33.3)	4 (10.8)
Adverse events that resulted in death	0	0
Adverse events that led to treatment discontinuation	4 (11.1)	NA
Adverse events that led to delay in treatment	26 (72.2)	NA
Adverse events that led to dose reduction	8 (22.2)	NA

NA, not applicable

All grades of adverse events that occurred at a higher incidence in the trabectedin group than in the BSC group by ≥20% were nausea (88.9% and 8.1% in the trabectedin and BSC groups, respectively; the same applies hereinafter in this paragraph), neutrophil count decreased (83.3% and 0%), ALT increased (66.7% and 0%), decreased appetite (58.3% and 5.4%), constipation (58.3% and 0%), white blood cell count decreased (55.6% and 0%), AST increased (47.2% and 0%), malaise (44.4% and 0%), vomiting (41.7% and 0%), platelet count decreased (36.1% and 0%), anaemia (30.6% and 2.7%), gamma-glutamyltransferase (GGT) increased (27.8% and 0%), myalgia (27.8%, 0%), pyrexia (25.0% and 2.7%), diarrhoea (22.2% and 0%), and lymphocyte count decreased (22.2% and 0%). Grade 3 or higher adverse events that occurred at a higher incidence in the trabectedin group than in the BSC group by ≥10% were neutrophil count decreased (66.7% and 0%), ALT increased (61.1% and 0%), white blood cell count

decreased (55.6% and 0%), AST increased (41.7% and 0%), GGT increased (25.0% and 0%), lymphocyte count decreased (22.2% and 0%), anaemia (19.4% and 2.7%), platelet count decreased (16.7% and 0%), and febrile neutropenia (13.9% and 0%).

Serious adverse events occurred in 12 of 36 subjects (33.3%) in the trabectedin group, and 4 of 37 subjects (10.8%) in the BSC group. Serious adverse events that occurred in ≥2 subjects were febrile neutropenia (5 subjects, 13.9%), and platelet count decreased (2 subjects, 5.6%) in the trabectedin group, but there were no serious adverse events that occurred in ≥2 subjects in the BSC group.

Adverse events that led to treatment discontinuation occurred in 4 of 36 subjects (11.1%) in the trabectedin group, and among these adverse events, platelet count decreased (2 subjects) is the only adverse event occurred in ≥2 subjects.

Different dose levels were used in the Japanese and foreign clinical studies, which hinders a strict comparison of safety profiles between the Japanese and non-Japanese populations. However, because of the limited data available on trabectedin treatment in Japanese patients with STS, PMDA asked the applicant to explain the differences in safety profiles between the Japanese and non-Japanese populations.

The applicant's explanation:
The pooled analysis data from 73 patients who received 1.2 mg/m^2 of trabectedin as a starting dose in Studies 10045030, 10045040, and 10045020 (the pooled analysis of the Japanese studies) were compared with the data of Study ET743-STS-201, in which 1.5 mg/m^2 of trabectedin was administered as a starting dose.

Adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥10% are shown in the table below.

Adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥10% (pooled analysis of the Japanese studies and Study ET743-STS-201)

Preferred term	Number of subjects (%)			
	Japanese patients 73 subjects		Non-Japanese patients 130 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Nausea	67 (91.8)	4 (5.5)	98 (75.4)	7 (5.4)
Neutrophil count decreased*	64 (87.7)	56 (76.7)	75 (57.7)	56 (43.1)
ALT increased	52 (71.2)	49 (67.1)	72 (55.4)	52 (40.0)
White blood cell count decreased	47 (64.4)	45 (61.6)	11 (8.5)	5 (3.8)
Decreased appetite	46 (63.0)	9 (12.3)	11 (8.5)	0
Constipation	44 (60.3)	1 (1.4)	45 (34.6)	0
AST increased	43 (58.9)	35 (47.9)	63 (48.5)	30 (23.1)
Malaise	40 (54.8)	1 (1.4)	3 (2.3)	0
GGT increased	28 (38.4)	25 (34.2)	5 (3.8)	2 (1.5)
Platelet count decreased	28 (38.4)	15 (20.5)	7 (5.4)	1 (0.8)
Lymphocyte count decreased	20 (27.4)	17 (23.3)	2 (1.5)	1 (0.8)
Febrile neutropenia	11 (15.1)	11 (15.1)	2 (1.5)	1 (0.8)
Stomatitis	11 (15.1)	0	4 (3.1)	0
Tumor pain	10 (13.7)	2 (2.7)	0	0

MedDRA versions used for the studies: MedDRA/J ver.16.1 for the pooled analysis of the Japanese studies, and MedDRA/J ver.8.0 for Study ET743-STS-201. *, In the data for non-Japanese patients, neutropenia was included in "neutropenia count decreased."

Serious adverse events that occurred at a higher incidence in Japanese subjects than in non-Japanese subjects by ≥2% were febrile neutropenia (12.3% and 0% in Japanese and non-Japanese subjects, respectively; the same applies hereinafter in this section), platelet count decreased (5.5% and 0%), decreased appetite (5.5% and 0%), ALT increased (2.7% and 0%), and AST increased (2.7% and 0%).

The adverse event leading to dose reduction that occurred at a higher incidence in Japanese subjects than in non-Japanese subjects by ≥2% was platelet count decreased (5.5% and 0%). Adverse events leading to treatment discontinuation that occurred at a higher incidence in Japanese subjects than in non-Japanese subjects by ≥2% were platelet count decreased (2.7% and 0%), nausea (2.7% and 0%), and decreased appetite (2.7% and 0%).

Furthermore, serious adverse events that occurred only in Japanese subjects were disease progression (2 of 73 subjects, 2.7%), colitis (1 of 73 subjects, 1.4%), and rhabdomyolysis (1 of 73 subjects, 1.4%).

PMDA's view:

In Study 10045030, although the incidences of ≥ Grade 3 adverse events and serious adverse events were higher in the trabectedin group than in the BSC group, there were no adverse events that resulted in death, and adverse events were manageable by appropriate measures including treatment interruption and dose reduction; therefore, trabectedin can be well tolerated provided appropriate measures are taken such as treatment interruption, dose reduction, and treatment discontinuation. However, when administering trabectedin, close attention should be paid especially to the following ≥ Grade 3 adverse events that occurred at a higher incidence in the trabectedin group than in BSC group including: anaemia,

febrile neutropenia, ALT increased, AST increased, GGT increased, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, and white blood cell count decreased; and it is necessary to provide information on the status of occurrence of these adverse events to healthcare professionals in an appropriate manner.

It is difficult to strictly compare safety profiles between the Japanese and non-Japanese populations because of differences in the dose levels used in the Japanese and foreign clinical studies. Nevertheless, except for nausea and decreased appetite, adverse events that occurred at a higher incidence in Japanese subjects than in non-Japanese subjects, and that were considered to require close attention in view of the incidence of ≥ Grade 3 adverse events were the same as the events considered to require close attention based on the results of Study 10045030.

The following sections discuss adverse events that have been listed as requiring caution in the package inserts for trabectedin in other countries, in addition to the above-mentioned adverse events considered to require close attention when administering trabectedin.

4.(iii).B.(3).2) Bone marrow depression and febrile neutropenia

The applicant explained the occurrence of bone marrow depression (neutrophil count decreased, lymphocyte count decreased, platelet count decreased, and anaemia) and febrile neutropenia related to administration of trabectedin.

The applicant's explanation:

In the pooled analysis of the Japanese studies, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, anaemia, and febrile neutropenia occurred in 64 of 73 subjects (87.7%), 20 of 73 subjects (27.4%), 28 of 73 subjects (38.4%), 24 of 73 subjects (32.9%), and 11 of 73 subjects (15.1%), respectively, and among these, ≥ Grade 3 adverse events occurred in 56 of 73 subjects (76.7%), 17 of 73 subjects (23.3%), 15 of 73 subjects (20.5%), 16 of 73 subjects (21.9%), and 11 of 73 subjects (15.1%), respectively. Serious adverse events were febrile neutropenia (9 subjects), platelet count decreased (4 subjects), and anaemia (5 subjects), and a causal relationship to trabectedin could not be ruled out in any of these events except for anaemia in 1 subject. Adverse events that led to treatment discontinuation were platelet count decreased (2 subjects) and febrile neutropenia (1 subject), and a causal relationship to trabectedin could not be ruled out in any of these events. Adverse events that led to dose reduction were neutrophil count decreased (5 subjects), platelet count decreased (3 subjects), anaemia (2 subjects), and febrile neutropenia (1 subject), and a causal relationship to trabectedin could not be ruled out in any of these events.

PMDA asked the applicant to explain the onset time of febrile neutropenia, and status of occurrence of infections (other than febrile neutropenia).

The applicant's explanation:

In the pooled analysis of the Japanese studies, febrile neutropenia occurred in 7 of 11 subjects (63.6%) by the end of Cycle 2, and the median time to the first onset was 44 days (range, 7 to 403 days). Three patients had febrile neutropenia that resulted in death in foreign phase II studies (1 subject each in Studies ET-B-005-98, ET-B-008-98, and ET-B-023-00).

In the pooled analysis of the Japanese studies, infections occurred in 25 of 73 subjects (34.2%), and among these, there was only one case of ≥ Grade 3 adverse event (pneumonia in 1 of 73 subjects, 1.4%). In 4 patients, adverse events of septic shock resulted in death (i.e., 2 subjects in Study ET743-STS-201 and 1 subject each in Studies ET-B-023-00 and ET-B-010-99).

With regard to trabectedin-related febrile neutropenia, PMDA asked the applicant to explain the situation of prophylactic administration of granulocyte colony-stimulating factors (G-CSFs) or antibacterial agents in clinical studies, as well as measures to prevent febrile neutropenia.

The applicant's explanation:
Patients were not allowed to use primary prophylactic G-CSF, and actually no patients received prophylactic G-CSF in the Japanese clinical studies (Studies 10045020, 10045030, and 10045040); therefore, the efficacy of primary prophylactic G-CSFs against trabectedin-related febrile neutropenia is unknown. However, the incidence of trabectedin-related febrile neutropenia was 15.1% in the pooled analysis of the Japanese studies. Moreover, *the Guidelines for proper use of G-CSF*, 2013 edition (edited by Japan Society of Clinical Oncology, published by Kanehara & Co., Ltd.;2013) (G-CSF Guidelines) recommend that the use of primary prophylactic G-CSFs should be considered when patients at a higher risk of severe febrile neutropenia (e.g., advanced age) undergo chemotherapy expected to induce febrile neutropenia at an incidence of 10% to 20%. Based on the above, the use of primary prophylactic G-CSF should be recommended when trabectedin is administered to such patients.

The protocols of the Japanese clinical studies (Studies 10045020, 10045030, and 10045040) did not specify any criteria for prophylactic administration of antibacterial agents; therefore, no information concerning the objectives of the use of antibacterial agents were collected. For this reason, it is difficult to evaluate the efficacy of prophylactic administration of antibacterial agents against febrile neutropenia.

PMDA's view:
In the Japanese clinical studies, incidences of bone marrow depression and febrile neutropenia were high in the trabectedin group, and serious events were also observed; therefore, special attention is required especially for bone marrow depression and febrile neutropenia when administering trabectedin. Furthermore, deaths due to septic shock have been reported in foreign clinical studies; therefore, vigilance is needed for the possible onset of infections.

Based on the above, information on the status of occurrence of bone marrow depression and febrile neutropenia in the clinical studies should be provided to healthcare professionals in an appropriate

manner. At the same time, hematological examinations should be performed on a periodic basis when administering trabectedin. The criteria for dose reduction, treatment interruption, and treatment discontinuation used in the clinical studies should be included in the package insert and other relevant materials to ensure that physicians can respond appropriately to bone marrow depression.

4.(iii).B.(3).3) Hepatic dysfunction

The applicant's explanation on trabectedin-related hepatic dysfunction:

All the adverse events classified under the MedDRA System Organ Class (SOC) "Hepatobiliary disorders" and the following MedDRA preferred terms (PTs) were collected: ALT increased, AST increased, GGT increased, blood alkaline phosphatase (ALP) increased, blood bilirubin increased, blood lactate dehydrogenase increased, and blood cholesterol increased.

The table below shows the incidence of hepatic dysfunction in the pooled analysis of the Japanese studies.

The occurrence of hepatic dysfunction (pooled analysis of the Japanese studies)

Preferred term (MedDRA/J Ver.16.1)	Number of subjects (%)			
	Trabectedin 73 subjects		BSC 37 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Hepatic dysfunction	54 (74.0)	52 (71.2)	0	0
ALT increased	52 (71.2)	49 (67.1)	0	0
AST increased	43 (58.9)	35 (47.9)	0	0
GGT increased	28 (38.4)	25 (34.2)	0	0
Blood ALP increased	11 (15.1)	2 (2.7)	0	0
Blood bilirubin increased	7 (9.6)	0	0	0
Blood lactate dehydrogenase increased	2 (2.7)	0	0	0
Blood cholesterol increased	1 (1.4)	1 (1.4)	0	0

Serious hepatic dysfunction (ALT increased/AST increased) occurred in 2 subjects in the trabectedin group. Hepatic dysfunction that led to dose reduction, treatment interruption, and treatment discontinuation occurred in 1 of 73 subjects (1.4%), 22 of 73 subjects (30.1%), and 1 of 73 subjects (1.4%), respectively, in the trabectedin group.

The median time to the first onset of hepatic dysfunction was 3.0 days (range, 2 to 79 days).

There were no liver injuries that meet the criteria of Hy's law (defined based on the *Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, U.S. Department of Health and Human Services, Food and Drug Administration;2009).

Hepatic failure occurred in 1 subject in a foreign phase II study (Study ET-B-028-06) while there were no events of hepatic failure in the pooled analysis of the Japanese studies. The overseas post-marketing

surveillance has reported 14 adverse events of hepatic failure, 4 of which resulted in death. A causal relationship to trabectedin could not be ruled out in any of these events.

PMDA's view:

With regard to trabectedin-related hepatic dysfunction, the incidence of ≥ Grade 3 adverse events was high, and serious events have also been reported. In addition, events of hepatic failure resulting in death have been reported in the overseas post-marketing surveillance; therefore, hepatic dysfunction-associated adverse events require close attention when administering trabectedin. During treatment with trabectedin, liver function tests should be monitored on a regular basis, and appropriate measures including treatment discontinuation should be taken if abnormalities are observed in the test values. To this end, it is necessary to provide information including the frequency of liver function tests and criteria for treatment interruption specified in the clinical study protocols in the package insert and other relevant materials. It is also necessary to provide information on the status of occurrence (e.g., onset time, severity, and response measures) of hepatic dysfunction in the clinical studies in an appropriate manner to healthcare professionals, especially the fact that the onset of hepatic dysfunction occurred relatively quickly in some patients in the clinical studies, as early as 3 days after administration.

4.(iii).B.(3).4) Gastrointestinal disorders

The applicant's explanation on trabectedin-related gastrointestinal disorders:

Adverse events classified under the MedDRA SOC "Gastrointestinal disorders" were collected as adverse events associated with gastrointestinal disorder.

The table below shows the incidence of gastrointestinal disorders in the pooled analysis of the Japanese studies.

Gastrointestinal disorders with an incidence of ≥2% in the trabectedin group (pooled analysis of the Japanese studies)

Preferred term (MedDRA/J Ver.16.1)	Number of subjects (%)			
	Trabectedin 73 subjects		BSC 37 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Gastrointestinal disorders	71 (97.3)	7 (9.6)	0 (0)	0 (0)
Nausea	67 (91.8)	4 (5.5)	0	0
Constipation	44 (60.3)	1 (1.4)	0	0
Vomiting	32 (43.8)	0	0	0
Diarrhoea	13 (17.8)	1 (1.4)	0	0
Stomatitis	11 (15.1)	0	0	0
Abdominal discomfort	4 (5.5)	0	0	0
Abdominal pain upper	3 (4.1)	0	0	0
Dyspepsia	3 (4.1)	0	0	0
Colitis	2 (2.7)	0	0	0

Serious gastrointestinal disorders occurred in 3 of 73 subjects (4.1%; colitis, nausea, and subileus in 1 subject each) in the trabectedin group. No treatment delay or dose reduction occurred due to

gastrointestinal disorders. Gastrointestinal disorders led to treatment discontinuation in 2 of 73 subjects (2.7%; nausea, and nausea/vomiting in 1 subject each) in the trabectedin group.

PMDA's view:
Since trabectedin-related gastrointestinal disorders occurred at a high frequency, and serious events have also been reported, close attention should be paid to the possible occurrence of these adverse events when administering trabectedin. Therefore, it is necessary to provide information on the status of occurrence of gastrointestinal disorders in the clinical studies to those engaged in healthcare practice in an appropriate manner.

4.(iii).B.(3).5) Rhabdomyolysis

The applicant's explanation on trabectedin-related rhabdomyolysis:
The table below summarizes the characteristics of patients who experienced rhabdomyolysis in the Japanese clinical studies (Studies 10045020, 10045030, and 10045050). All 3 patients had serious adverse events leading to discontinuation of trabectedin. In 1 patient (Study 10045050), Grade 3 creatinine increased occurred following the onset of rhabdomyolysis.

Patients with rhabdomyolysis (Studies 10045020, 10045030, and 10045050)

Study	Dose (mg/m^2)	Sex	Age (years)	ECOG PS	Grade	Onset (days)	Duration (days)	Seriousness	Outcome	Causality
10045020	1.5	M	55	0	3	36	29	Serious	Recovered	Related
10045030	1.2	M	37	1	4	36	23	Serious	Recovered	Related
10045050	1.2	M	53	1	4	36	104	Serious	Not recovered	Related

The foreign clinical studies and foreign post-marketing surveillance have reported 122 adverse events of rhabdomyolysis, 34 of which resulted in death.

The onset time of rhabdomyolysis was studied in 83 subjects whose onset times were known using the data from Japanese and foreign clinical studies and foreign post-marketing surveillance reports. Of the 83 subjects, 16 (19.3%) experienced rhabdomyolysis in Cycle 1, 48 (57.8%) in Cycle 2, 12 (14.5%) in Cycle 3, and 7 (8.4%) in Cycle 4 or later.

PMDA's view:
The Japanese clinical studies have reported that 3 patients experienced trabectedin-related serious rhabdomyolysis; the foreign clinical studies and foreign post-marketing surveillance have reported rhabdomyolysis resulting in death. Given this, close attention should be paid to the possible occurrence of rhabdomyolysis when administering trabectedin. Therefore, it is necessary to provide information on the status of occurrence of rhabdomyolysis in the clinical studies to healthcare professionals in an appropriate manner, and provide a caution in the package insert and other relevant materials to ensure that the condition of patients is carefully observed and CPK is closely monitored on a regular basis

during treatment with trabectedin, and if abnormalities are detected, appropriate measures should be taken including discontinuing treatment with trabectedin.

4.(iii).B.(3).6) Injection site reactions

The applicant's explanation on trabectedin-related injection site reactions:

Adverse events classified under the following MedDRA preferred terms were collected as injection site reactions: administration site pain, application site haemorrhage, application site erythema, application site excoriation, application site irritation, application site oedema, application site pain, catheter site effusion, catheter site erythema, catheter site haematoma, catheter site haemorrhage, catheter site inflammation, catheter site necrosis, catheter site oedema, catheter site pain, catheter site phlebitis, catheter site pruritus, catheter site rash, catheter site related reaction, chemotherapy extravasation management, extravasation, implant site necrosis, infusion site bruising, infusion site erosion, infusion site erythema, infusion site extravasation, infusion site granuloma, infusion site induration, infusion site inflammation, infusion site irritation, infusion site mass, infusion site necrosis, infusion site oedema, infusion site pain, infusion site swelling, infusion site ulcer, injection site dermatitis, injection site discomfort, injection site erosion, injection site erythema, injection site extravasation, injection site granuloma, injection site haemorrhage, injection site induration, injection site inflammation, injection site irritation, injection site joint effusion, injection site joint pain, injection site joint swelling, injection site mass, injection site necrosis, injection site nodule, injection site oedema, injection site pain, injection site phlebitis, injection site pruritus, infusion site reaction, injection site swelling, injection site ulcer, skin necrosis, and soft tissue necrosis.

In the pooled analysis of the Japanese studies, Grade 1 injection site reaction was observed in 1 of 73 subjects (1.4%). In the foreign clinical studies, serious injection site reactions occurred in 5 patients who received trabectedin via the central vein. Foreign post-marketing surveillance revealed that 1 patient experienced skin necrosis due to extravasation of trabectedin, resulting in skin grafting.

PMDA's view:

According to the pooled analysis of the Japanese studies, no patients experienced trabectedin-induced serious injection site reactions in Japan. However, serious injection site reactions (e.g., the case resulting in skin grafting) have been reported in foreign clinical studies and foreign post-marketing surveillance. Furthermore, local irritation at the administration site was noted in the non-clinical studies [see "3.(iii).A.(6) Local tolerance"]. Patients should thus be monitored closely for injection site reactions when trabectedin is administered. Therefore, it is necessary to provide information on the status of occurrence of injection site reactions to healthcare professionals in an appropriate manner, and provide a caution in information materials so that injection sites are monitored on a regular basis during treatment with trabectedin, and if extravasation is detected, appropriate measures should be taken.

4.(iii).B.(3).7) Others

According to foreign clinical data, (a) hypersensitivity, (b) secondary malignancy, and (c) pancreatitis are expected to be induced by trabectedin. The applicant explained the status of occurrence of these events in the foreign clinical studies and post-marketing experiences.

(a) Hypersensitivity

One patient experienced hypersensitivity according to foreign post-marketing surveillance. The patient experienced erythema facial within 5 minutes after the start of administration in Cycle 2, followed by hypotension with absent pulse, bronchospasm, and apnoea, resulting in death.

(b) Secondary malignancy

The following adverse events have been reported in foreign clinical studies and foreign post-marketing surveillance: myelodysplastic syndrome (12 patients), acute myeloid leukaemia (9 patients), leukaemia (5 patients), myeloid leukaemia (2 patients), malignant melanoma (2 patients), acute monocytic leukaemia (1 patient), acute leukaemia (1 patient), oesophageal squamous cell carcinoma (1 patient), squamous cell carcinoma of the tongue (1 patient), and squamous cell carcinoma (1 patient).

(c) Pancreatitis

The following adverse events have been reported in foreign clinical studies not included in the submitted application data: pancreatitis (8 subjects), lipase increased (6 subjects), amylase increased (4 subjects), and pancreatitis acute (2 subjects).

PMDA's view:

Given that serious adverse events have been reported in foreign clinical studies and in foreign post-marketing surveillance, as described in (a), (b), and (c), it is necessary to provide any relevant information currently available to healthcare professionals in an appropriate manner. Data should be continuously collected after trabectedin is released to the Japanese market, and when new safety findings become available, it is necessary to provide the information to healthcare professionals in an appropriate manner.

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

The proposed indications of trabectedin are shown below. In the "Precautions for indications" section, the following advice was included: (a) The efficacy and safety of trabectedin have not been established in chemotherapy-naïve patients. (b) Prior to determining whether a patient is eligible for trabectedin therapy, carefully read the "Clinical studies" section of the package insert to obtain information including the histological subtypes of patients enrolled in clinical studies.

Indications

Soft tissue sarcomas of the following histological subtypes: myxoid/round cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, extra-osseous Ewing's sarcoma/primitive neuroectodermal

tumor, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, alveolar soft part sarcoma, clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, giant cell fibroblastoma, and endometrial stromal sarcoma.

Based on the discussions in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" and in the following sections, PMDA concluded that it is appropriate to set the indication for trabectedin as "soft tissue sarcomas," and at the same time to provide information in the "Clinical studies" section of the package insert regarding the histopathological subtypes and history of chemotherapy treatment of patients analyzed in Study 10045030, and include the following points in the "Precautions for indications" section.

- The efficacy and safety of trabectedin have not been established in chemotherapy-naïve patients.
- The efficacy and safety of trabectedin have not been established in patients with histopathological subtypes not evaluated in the clinical studies.
- Prior to determining whether a patient is eligible for trabectedin therapy, carefully read the "Clinical studies" section of the package insert, fully understand the efficacy and safety of trabectedin, and carefully consider other treatment options.

Clinical positioning of trabectedin and intended patient population

Trabectedin is described as follows in diagnostic guidelines in the US and Europe, and major textbooks on oncology in and outside Japan.

Diagnostic guidelines:

- The US's National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma (v.1.2015):

  Trabectedin showed therapeutic effects in some patients with unresectable STS in foreign phase II studies (e.g., *J Clin Oncol.* 2009;27:4188-96). A foreign phase III trial (Study ET-C-002-07) was conducted in chemotherapy-naïve patients with unresectable STS of histopathological subtypes reported as carrying chromosomal translocations, to compare the efficacy and safety of trabectedin with those of DOX-based chemotherapy, and the results did not show improvement in PFS or OS by administration of trabectedin (*Eur J Cancer.* 2014;50:1137-47).
- The "Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" issued by the European Society for Medical Oncology (ESMO) (*Ann Oncol*. 25 Suppl 3:2014;iii102–12):

  Trabectedin is an option for patients with unresectable STS previously treated with chemotherapy. Trabectedin has been shown to be effective and safe in the treatment of leiomyosarcoma and liposarcoma, and have clinical benefits also for other histological subtypes of STS.

Textbooks:

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 10th edition (Lippincott Williams & Wilkins 2014; PA, USA):
  Patients with unresectable STS of various histological subtypes responded to trabectedin therapy in foreign phase II studies (*Future Oncol.* 2007;3:381-92); a foreign phase III study in patients with unresectable liposarcoma and leiomyosarcoma previously treated with chemotherapy is underway to compare the efficacy and safety of trabectedin with those of dacarbazine.
- The publication of the Japanese Society of Medical Oncology, *New Clinical Oncology for Cancer Medication Specialists* 3rd ed. (Nankodo Co., Ltd., 2012):
  In phase II studies, trabectedin was effective in some patients with unresectable STS previously treated with chemotherapy. A foreign phase III study in patients with unresectable STS previously treated with anthracyclines-based chemotherapy is underway to compare the efficacy and safety of trabectedin with those of dacarbazine.

PMDA asked the applicant to explain the clinical positioning of trabectedin in the treatment of unresectable STS, and the eligibility of patients for trabectedin therapy.

The applicant's explanation:
Study 10045030 enrolled patients previously treated with chemotherapy for unresectable STS of histological subtypes reported to carry chromosomal translocations, because trabectedin had been reported to be effective in such patients (e.g., *Lancet Oncol.* 2007;8:595-602). The study demonstrated clinical benefits of trabectedin, suggesting that trabectedin is a treatment option for the patient population eligible for Study 10045030.

PMDA asked the applicant to discuss trabectedin therapy in the following patients: (a) Patients with STS of the following histological subtypes: dermatofibrosarcoma protuberans, angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, low-grade fibromyxoid sarcoma, giant cell fibroblastoma, endometrial stromal sarcoma, and desmoplastic small round cell tumor. These subtypes were eligible for Study 10045030, but the efficacy for these subtypes could not be fully evaluated based on the results of the study. (b) Patients with STS of certain histological subtypes excluded from Study 10045030.

The applicant's response:
Trabectedin is recommended for the patients in (a), for reasons listed below, while it is not recommended for patients in (b) at this point. Meanwhile, a foreign phase III study (Study ET743-SAR-3007) is ongoing to assess the efficacy and safety of trabectedin in patients with certain histological subtypes of STS that were excluded from Study 10045030, given that trabectedin has been demonstrated to have antiproliferative effects on STS cell lines for liposarcoma, leiomyosarcoma, and other subtypes in the non-clinical study [see "3.(i).A.(1).2) Effects on STS cell lines"]. Based on the results of Study ET743-SAR-3007, the applicant will formulate a development plan for trabectedin targeting certain histological subtypes of STS that were not included in Study 10045030.

(a) Trabectedin is expected to be effective taking the following points into account:
- In Study 10045030, 1 patient with dermatofibrosarcoma protuberans had a PFS of 1.9 months after trabectedin therapy. The patient had had a PFS of 1.0 month after the previous treatment with DOX. Thus, trabectedin was not inferior to DOX in efficacy.
- The median PFS was 7.5 months in 1 patient with angiomatoid fibrous histiocytoma and 10.2 months in 2 patients with extraskeletal myxoid chondrosarcoma. These values were higher than the median PFS (5.6 months) in patients receiving trabectedin in Study 10045030.
- Desmoplastic small round cell tumor has been reported to respond to trabectedin (*Antiacancer Res*. 2014;34: 3683-8; *Clin Sarcoma Res*. 2014;4:3).

(b) There are only a few studies that enrolled patients with STS of certain histological subtypes excluded from Study 10045030. At this point, the efficacy of trabectedin in such patients is thus unknown.

Furthermore, given that pazopanib hydrochloride (pazopanib) has been approved for the use in STS patients previously treated with DOX-based or other chemotherapy, PMDA asked the applicant to explain when to use trabectedin and when to use pazopanib.

The applicant's explanation:
A global phase III study (Study VEG110727) demonstrated the clinical benefit of pazopanib. This study did not enroll patients with the following histological subtypes (although these subtypes were evaluated in Study 10045030): myxoid/round cell liposarcoma, alveolar rhabdomyosarcoma, extra-osseous Ewing's sarcoma/primitive neuroectodermal tumor, dermatofibrosarcoma protuberans, angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma, and mesenchymal chondrosarcoma. Since the clinical benefit of pazopanib in the treatment of the above histological subtypes is unknown, trabectedin is considered to be a more preferable option for these subtypes.

Among the histological subtypes included in Study 10045030, those other than the above were included in both Studies VEG110727 and 10045030; however, so far there have been no study results comparing the efficacy and safety of trabectedin and pazopanib in patients with these histological subtypes. Therefore, for patients with such histological subtypes, physicians are expected to choose either trabectedin or pazopanib depending on the patient's condition.

PMDA's view:
Although the applicant's explanation regarding patients with the histological subtypes of STS in (a) does not go beyond speculation, trabectedin can be regarded as a new treatment option for patients with these histological subtypes, taking the following points into consideration; therefore, PMDA largely accepted the above explanation by the applicant.

- Given the diversity and rare incidence of STS histological subtypes, it is difficult to evaluate the efficacy of trabectedin on a subtype-by-subtype basis in clinical studies.
- Treatment options for patients with STS of these histological subtypes are extremely limited.

In addition, given that trabectedin is to be administered by physicians with sufficient knowledge and experience in cancer chemotherapy, PMDA concluded that the indication for trabectedin can be defined as "soft tissue sarcomas," provided that the "Clinical studies" section of the package insert includes description regarding the histopathological subtypes and history of chemotherapy in patients evaluated in Study 10045030, and that the following points are advised in the "Precautions for indication" section.

- The efficacy and safety of trabectedin have not been established in chemotherapy-naïve patients.
- The efficacy and safety of trabectedin have not been established in patients with histopathological subtypes not evaluated in the clinical studies.
- Prior to determining whether a patient is eligible for trabectedin therapy, carefully read the "Clinical studies" section of the package insert, fully understand the efficacy and safety of trabectedin, and carefully consider other treatment options.

The clinical benefit of trabectedin for patients with the histological subtypes described in (b) above will be clarified when the results of Study ET743-SAR-3007 become available.

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

The proposed dosage and administration for trabectedin was as follows: "The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition." In the proposed "Precautions for dosage and administration" section, the following points were specified.

- The efficacy and safety of trabectedin co-administered with other antineoplastic agents have not been established.
- To prevent or alleviate hepatic dysfunction, nausea, or vomiting associated with trabectedin, DEX and a selective serotonin receptor ($5\text{-}HT_3$ receptor) antagonist antiemetic agent should be administered 30 minutes before administration of trabectedin.
- Trabectedin should be administered via the central vein.
- Dose reduction should be considered in patients with hepatic impairment.
- Criteria for treatment interruption, dose reduction, and treatment discontinuation in case of adverse reactions.

Based on the discussion in the section "4.(ii).B.(2) Effects of decreased hepatic function on the PK of trabectedin" and the following sections, PMDA agreed on the proposed dosage and administration ("The usual adult dosage is 1.2 mg/m^2 [body surface area] of trabectedin, administered as an intravenous

infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition."), concluding that the following points should be specified in the "Precautions for dosage and administration" section:

- The efficacy and safety of trabectedin co-administered with other antineoplastic agents have not been established.
- Trabectedin should be administered via the central vein.
- Criteria for administration and dose reduction in case of adverse events.

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

The applicant's explanation on the rationale for selecting the dosage and administration for trabectedin:
The dosage regimen for Study 10045030 was selected based on the results of the clinical studies listed below. The results of Study 10045030 demonstrated the clinical benefit of trabectedin; therefore, the dosage and administration of trabectedin was proposed as described above based on the dosage regimen for Study 10045030. At the same time, a caution that trabectedin needs to be administered via the central vein was included in the "Precautions for dosage and administration" section.

- The foreign phase II study (Study ET743-STS-201) showed that TTP was longer in the Q3W-24h group than in the QW-3h group, suggesting that trabectedin was expected to be more effective if administered as a 24-hour infusion than as a 3-hour infusion [see "4.(iii).A. Reference data (2).1) Foreign phase II study"].
- In the Japanese phase I study (Study 10045020), the recommended dosage regimen in Japanese patients with STS was 1.2 mg/m^2 of trabectedin, administered as a 24-hour intravenous infusion every 3 weeks [see "4.(iii).A. Evaluation data (1).1) Japanese phase I study"].
- In Japanese clinical studies, trabectedin was administered via the central vein. There was only 1 case of Grade 1 injection site reaction in 1 of 36 subjects (2.8%) in Study 10045030, and no tissue disorder caused by extravasation of trabectedin was observed. In the foreign phase I study (Study ET-A-001-95), phlebitis occurred in 8 of 12 subjects (66.7%) who received trabectedin as a 3-hour infusion through a peripheral vein. Based on the results of Study ET-A-001-95, it was recommended that trabectedin be administered via the central vein in clinical studies conducted thereafter. Administration of trabectedin via the central vein is also strongly recommended in the package inserts in other countries.

PMDA accepted the applicant's explanation.

4.(iii).B.(5).2) Criteria for treatment interruption, dose reduction, and treatment discontinuation

The applicant's explanation on the criteria for treatment interruption, dose reduction, and treatment discontinuation:

In Study 10045030, detailed criteria were defined for treatment interruption, dose reduction, and treatment discontinuation, and trabectedin was well tolerated when administered according the criteria. Therefore, the proposed "Precautions for dosage and administration" section provides criteria for starting treatment and reducing the dose, in accordance with the criteria for treatment interruption, dose reduction, and treatment discontinuation used in Study 10045030.

PMDA's view:
Given that trabectedin is to be administered by physicians with sufficient knowledge and experience in chemotherapy, the applicant's explanation is acceptable. The proposed criteria for treatment interruption, dose reduction, and treatment discontinuation (in the new drug application) should be tabulated as shown below. These criteria should be provided in the "Precautions for dosage and administration" section.

- If the laboratory values prior to starting treatment with trabectedin do not meet the following criteria, trabectedin should not be administered, or treatment should be delayed until the criteria are met.

Criteria for starting treatment with trabectedin

Parameter	Criteria
Neutrophil count	≥1500/mm^3
Haemoglobin	≥9.0 g/dL
Platelet count	≥10 × 10^4/mm^3
Albumin	≥2.5 g/dL
Bilirubin total	≤1.5 mg/dL
AST (GOT)	≤2.5 × upper limit of normal (ULN)
ALT (GPT)	
ALP*1	
CK (CPK)	
Creatinine clearance*2	≥30 mL/min

*1, This criterion does not apply if abnormal ALP is attributable to the primary disease.
*2, Values should be calculated according to the Cockcroft-Gault equation. If creatinine clearance is actually measured, the measured value must meet this criterion.

- In the event of an adverse reaction meeting the dose reduction criteria, the dose must be reduced by 1 level at a time, but not to less than 0.8 mg/m^2, the minimum dose.

Criteria for dose reduction

Parameter	Criteria
Neutrophil count	<500/mm^3 persisting for ≥6 days; or <500/mm^3 with fever or infection
Platelet count	<2.5 × 10^4/mm^3
Bilirubin total	>1.5 mg/dL
AST (GOT)	>2.5 × ULN on Day 21 or later
ALT (GPT)	
ALP	>2.5 × ULN
Non-hematological toxicity	≥ Grade 3*

* In accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Dose reduction levels

Reduction	Dose

Recommended dose	1.2 mg/m^2
First dose reduction	1.0 mg/m^2
Second dose reduction	0.8 mg/m^2

4.(iii).B.(5).3) Prophylactic administration of DEX and antiemetic 5-HT$_3$ receptor antagonists

Based on the discussions in the following sections (a) and (b), the applicant concluded that pretreatment with DEX and antiemetic 5-HT$_3$ receptor antagonist is expected to prevent hepatic dysfunction, nausea, and vomiting caused by trabectedin treatment; therefore, a statement on prophylactic administration is to be included in the "Precautions for dosage and administration" section.

(a) Prevention of hepatic dysfunction by DEX pretreatment

In a foreign phase II study (Study ET-B-010-99), prior to trabectedin treatment, subjects were pretreated with DEX and placebo in Cycles 1 and 2, respectively (the Dexa-Plac group), placebo and DEX in Cycles 1 and 2, respectively (the Plac-Dexa group), or DEX in both Cycles 1 and 2 (All-Dexa group). The incidences of blood bilirubin increased, AST increased, and ALT increased associated with administration of trabectedin in Cycles 1 and 2 are shown below.

In the Dexa-Plac group, the incidence of ≥ Grade 2 blood bilirubin increased was 5.3% and 12.5% in Cycles 1 and 2, respectively (the same applies hereinafter in this paragraph for the order of the cycles), ≥ Grade 3 AST increased was 31.6% and 68.8%, ≥ Grade 3 ALT increased was 47.4% and 75.0%; all events showed a higher incidence in Cycle 2 (placebo administered prior to trabectedin) than in Cycle 1. In the Plac-Dexa group, ≥ Grade 2 blood bilirubin increased was 37.5% and 0%, ≥ Grade 3 AST increased was 55.6% and 16.7%, and ≥ Grade 3 ALT increased was 55.6% and 16.7%; all events showed a higher incidence in Cycle 1 (placebo administered prior to trabectedin) than in Cycle 2. In the All-Dexa group, the incidence of ≥ Grade 2 blood bilirubin increased was 23.1% and 11.1%, ≥ Grade 3 AST increased was 38.5% and 11.1%, and ≥ Grade 3 ALT increased was 69.2% and 33.3%, suggesting that the incidence of each adverse event was lower in patients pretreated with DEX than in those receiving placebo before trabectedin therapy.

In a foreign compassionate use program for patients with unresectable STS, the effects of DEX pretreatment at 8 to 20 mg on the safety of trabectedin were assessed. The results showed that Grade 3 or 4 AST increased and ALT increased occurred in 1 of 31 patients (3.2%) in the DEX pretreatment group, and 16 of 23 patients (69.6%) in the group without DEX pretreatment, indicating that pretreatment with DEX can lower the incidence of trabectedin-related hepatic dysfunction (*Eur J Cancer.* 2006;42:1484-90).

Based on the above, pretreatment with DEX is considered to be effective in prevention of hepatic dysfunction associated with trabectedin.

(b) Prevention of nausea and vomiting by pretreatment with DEX and antiemetic 5-HT_3 receptor antagonist

The protocols of the Japanese clinical studies stipulated that patients must be pretreated with DEX and an antiemetic 5-HT_3 receptor antagonist. The results showed that the incidence of ≥ Grade 3 nausea/vomiting was low even though the incidence of nausea/vomiting in all grades was high [see "4.(iii).B.(3) Safety"]. This suggests that pretreatment with DEX and an antiemetic 5-HT_3 receptor antagonist is useful for the prevention of serious nausea/vomiting.

PMDA's view:

In Study ET-B-010-99, hepatic dysfunction occurred at a high incidence in the All-Dexa group; therefore, the applicant's comment that administration of DEX can prevent hepatic dysfunction is speculative.

Antiemetic therapy is recommended for patients receiving antineoplastic agents including trabectedin according to the emetic risk (*Guidelines for Appropriate Use of Antiemetics*, ver. 1.2, Japan Society of Clinical Oncology; 2014); therefore, prophylactic administration of DEX and an antiemetic 5-HT_3 receptor antagonist to patients receiving trabectedin would be a common treatment option adopted by physicians with sufficient knowledge and experience in chemotherapy.

Therefore, healthcare professionals should be informed, in an appropriate manner, that prophylactic administration of DEX and an antiemetic 5-HT_3 receptor antagonist was performed to patients receiving trabectedin in the Japanese clinical studies in order to prevent hepatic dysfunction and nausea/vomiting. However, it is not necessary to include a statement regarding these agents in the "Precautions for dosage and administration" section.

4.(iii).B. (5).4) Concomitant antineoplastic agents

The applicant explained that a cautionary statement to the effect that the efficacy and safety of trabectedin co-administered with another antineoplastic agent have not been established would be included in the package insert, because data from clinical studies evaluating the efficacy and safety of trabectedin in co-administered with other antineoplastic agents have not yet been obtained.

PMDA accepted the applicant's explanation.

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

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

A post-marketing surveillance will be conducted by the applicant in all patients with STS who receive trabectedin, to primarily investigate the safety of trabectedin in clinical use after the market launch.

Based on the status of occurrence of adverse reactions in the Japanese clinical studies, hepatic dysfunction, bone marrow depression, serious hypersensitivity, rhabdomyolysis or CPK increased, and injection site reactions were specified as priority investigation items. In addition, although trabectedin

is assumed to be primarily eliminated by hepatic metabolism [see "4.(ii).A.(2).3) Foreign phase I study"], it is unknown whether the safety of trabectedin depends on presence or absence of hepatic impairment because of the paucity of safety data in patients with hepatic impairment; accordingly, the presence or absence of hepatic impairment prior to trabectedin treatment was also set as a priority investigation item.

The target sample size was determined to be 150 patients based on the status of occurrence of adverse reactions in the pooled analysis of the Japanese studies.

The observation period was set at 48 weeks (a maximum of 16 cycles) for the following reasons: (1) The mean treatment period (mean number of cycles) was 18.9 weeks (6.3 cycles) in Study 10045030, and 17.0 weeks (5.7 cycles) in Study 10045040. (2) All adverse reactions developed by Week 45 (Cycle 15) after the start of treatment with trabectedin in the pooled analysis of the Japanese studies.

PMDA's view:
Because of the paucity of safety data in Japanese patients with STS who received trabectedin, it is necessary to collect safety data quickly in an unbiased manner after the market launch through a surveillance covering all patients who receive trabectedin, and to promptly provide the obtained safety information to healthcare professionals.

The incidence of ≥ Grade 3 adverse events of hepatic dysfunction and bone marrow depression was high relative to all grades, including serious events resulting in death, in the Japanese and foreign clinical studies. Given this, it is necessary to design the surveillance plan so that risk factors for these events can be assessed. With regard to the priority investigation items for the post-marketing surveillance, it should be ensured that data are also collected on hepatic failure and febrile neutropenia, which require special attention in treatment with trabectedin based on the clinical study results. On the other hand, serious hypersensitivity and injection site reaction have not been reported in the clinical studies in Japan. Even though data on these adverse events need to be collected through the post-marketing surveillance, it is not necessary to set these events as priority investigation items. The number of patients to be surveyed and the observation period should be re-examined to enable the assessment of the risk factors, taking account of the status of occurrence of the adverse events to be set as priority investigation items based on the above discussion.

4.(iii).B.(7) Development for pediatric patients

PMDA asked the applicant to explain the state of development of trabectedin dosage regimen for pediatric patients with STS.

The applicant's response:
A foreign phase II study (Study COG-ADVL0221) enrolled 50 subjects with STS (target population, patients 1 to 21 years of age),* but a therapeutic response was achieved by only 1 subject with

rhabdomyosarcoma (2.5%) among 40 subjects evaluable for efficacy (*Eur J Cancer.* 2012;48:579-85). Currently there is no plan in or outside Japan to develop trabectedin for the treatment of pediatric STS.

* Rhabdomyosarcoma (23 subjects), Ewing's sarcoma (16 subjects), alveolar soft part sarcoma (2 subjects), synovial sarcoma (2 subjects), spindle cell sarcoma (2 subjects), undifferentiated sarcoma (2 subjects), desmoplastic small round cell tumor (1 subject), unclassified sarcoma (1 subject), and sarcoma not otherwise specified (1 subject).

PMDA's view:

Only a limited number of agents have an approved dosage for pediatric patients with STS. The applicant should collect and analyze information on a demand for the development of trabectedin to treat pediatric patients , obtain information on development plans of trabectedin for pediatric use both in Japan and other countries without delay, and take appropriate measures for the development of dosage suitable for Japanese pediatric patients .

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

The data for deaths reported in the submitted clinical studies are presented in the "4.(iii) Summary of clinical efficacy and safety." The following sections summarize the main adverse events other than death observed in the studies.

4.(iv).(1) Japanese phase I study (10045020)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to trabectedin could not be ruled out also occurred in all subjects. The table below shows adverse events that occurred in ≥2 subjects in at least 1 group.

Adverse events that occurred in ≥2 subjects in at least 1 group

System Organ Class (SOC) Preferred term (MedDRA/J ver.16.1)	Number of subjects (%)					
	0.9 mg/m^2 3 subjects		1.2 mg/m^2 9 subjects		1.5mg/m^2 3 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	3 (100)	3 (100)	9 (100)	9 (100)	3 (100)	3 (100)
Blood and lymphatic system disorders						
Anaemia	0	0	6 (66.7)	2 (22.2)	2 (66.7)	2 (66.7)
Gastrointestinal disorders						
Constipation	2 (66.7)	0	6 (66.7)	0	3 (100)	0
Nausea	2 (66.7)	0	9 (100)	0	3 (100)	1 (33.3)
Stomatitis	0	0	2 (22.2)	0	0	0
Vomiting	2 (66.7)	0	6 (66.7)	0	2 (66.7)	0
General disorders and administration site conditions						
Malaise	1 (33.3)	0	6 (66.7)	1 (11.1)	3 (100)	0
Pyrexia	1 (33.3)	0	4 (44.4)	0	2 (66.7)	0
Infections and infestations						
Nasopharyngitis	0	0	3 (33.3)	0	0	0
Upper respiratory tract infection	0	0	2 (22.2)	0	0	0
Investigations						
ALT increased	2 (66.7)	1 (33.3)	9 (100)	8 (88.9)	3 (100)	3 (100)
AST increased	2 (66.7)	1 (33.3)	8 (88.9)	5 (55.6)	3 (100)	3 (100)
Blood CPK increased	1 (33.3)	0	3 (33.3)	1 (11.1)	2 (66.7)	2 (66.7)
Blood creatinine increased	0	0	1 (11.1)	0	2 (66.7)	0

System Organ Class (SOC) Preferred term (MedDRA/J ver.16.1)	Number of subjects (%)					
	0.9 mg/m^2 3 subjects		1.2 mg/m^2 9 subjects		1.5mg/m^2 3 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Electrocardiogram QT prolonged	0	0	2 (22.2)	0	1 (33.3)	1 (33.3)
GGT increased	0	0	6 (66.7)	4 (44.4)	3 (100)	2 (66.7)
Lymphocyte count decreased	0	0	6 (66.7)	3 (33.3)	3 (100)	1 (33.3)
Neutrophil count decreased	2 (66.7)	1 (33.3)	8 (88.9)	8 (88.9)	3 (100)	2 (66.7)
Platelet count decreased	0	0	4 (44.4)	3 (33.3)	3 (100)	3 (100)
White blood cell count decreased	0	0	8 (88.9)	6 (66.7)	3 (100)	2 (66.7)
Blood ALP increased	0	0	2 (22.2)	0	1 (33.3)	0
Metabolism and nutrition disorders						
Hypoalbuminaemia	2 (66.7)	0	1 (11.1)	0	0	0
Hypokalaemia	0	0	1 (11.1)	0	2 (66.7)	1 (33.3)
Decreased appetite	1 (33.3)	0	5 (55.6)	1 (11.1)	3 (100)	2 (66.7)
Musculoskeletal and connective tissue disorders						
Myalgia	0	0	2 (22.2)	0	2 (66.7)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
Tumour pain	0	0	2 (22.2)	0	0	0
Nervous system disorders						
Headache	0	0	4 (44.4)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 0.9 mg/m^2 group, 2 of 9 subjects (22.2%) in the 1.2 mg/m^2 group, and 3 of 3 subjects (100%) in the 1.5 mg/m^2 group. The serious adverse events were as follows: in the 0.9 mg/m^2 group, device-related infection (1 subject, 33.3%); in the 1.2 mg/m^2 group, platelet count decreased (2 subjects, 22.2%), febrile neutropenia, decreased appetite, and anaemia (1 subject each, 11.1%); and in the 1.5 mg/m^2 group, electrocardiogram QT prolonged, decreased appetite, rhabdomyolysis, and platelet count decreased, blood CPK increased, and bone marrow failure (1 subject each, 33.3%); and a causal relationship to the study drug could not be ruled out for any of these events.

Adverse events that led to treatment discontinuation occurred in 1 of 9 subjects (11.1%) in the 1.2 mg/m^2 group, and 2 of 3 subjects (66.7%) in the 1.5 mg/m^2 group. The adverse events that led to treatment discontinuation were neutropenia (1 subject, 11.1%) in the 1.2 mg/m^2 group; and rhabdomyolysis and platelet count decreased (1 subject each, 33.3%) in the 1.5 mg/m^2 group, and a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(2) Japanese phase II study (10045030)

Adverse events occurred in 36 of 36 subjects (100%) in the trabectedin group, and 24 of 37 subjects (64.9%) in the BSC group, and a causal relationship to the study drug could not be ruled out in any of these events in the trabectedin group (36 of 36 subjects, 100%). The table below shows adverse events with an incidence of ≥20% in at least 1 group.

Adverse events with an incidence of ≥20% in at least 1 group

System Organ Class (SOC) Preferred term (MedDRA/J ver.16.1)	Number of subjects (%)			
	Trabectedin 36 subjects		BSC 37 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	36 (100)	34 (94.4)	24 (64.9)	5 (13.5)
Blood and lymphatic system disorders				
Anaemia	11 (30.6)	7 (19.4)	1 (2.7)	1 (2.7)
Gastrointestinal disorders				
Constipation	21 (58.3)	0	0	0
Diarrhoea	8 (22.2)	1 (2.8)	0	0
Nausea	32 (88.9)	3 (8.3)	3 (8.1)	0
Vomiting	15 (41.7)	0	0	0
General disorders and administration site conditions				
Malaise	16 (44.4)	0	0	0
Pyrexia	9 (25.0)	0	1 (2.7)	0
Investigations				
ALT increased	24 (66.7)	22 (61.1)	0	0
AST increased	17 (47.2)	15 (41.7)	0	0
GGT increased	10 (27.8)	9 (25.0)	0	0
Lymphocyte count decreased	8 (22.2)	8 (22.2)	0	0
Neutrophil count decreased	30 (83.3)	24 (66.7)	0	0
Platelet count decreased	13 (36.1)	6 (16.7)	0	0
White blood cell count decreased	20 (55.6)	20 (55.6)	0	0
Metabolism and nutrition disorders				
Decreased appetite	21 (58.3)	3 (8.3)	2 (5.4)	0
Musculoskeletal and connective tissue disorders				
Myalgia	10 (27.8)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase

Serious adverse events occurred in 12 of 36 subjects (33.3%), and 4 of 37 subjects (10.8%) in the BSC group. The serious adverse events were as follows: in the trabectedin group, febrile neutropenia (5 subjects, 13.9%), platelet count decreased (2 subjects, 5.6%), deep vein thrombosis, decreased appetite, pneumonia, dyspnoea, anaemia, subileus, colitis, device-related infection, ALT increased, AST increased, and rhabdomyolysis (1 subject each, 2.8%); in the BSC group, tumour pain, arthritis, ileus, and disease progression (1 subject each, 2.7%). Among these events, a causal relationship to the study drug could not be ruled out in the following events in the trabectedin group: febrile neutropenia (5 subjects), platelet count decreased (2 subjects), decreased appetite, pneumonia, anaemia, colitis, ALT increased, AST increased, rhabdomyolysis (1 subject each).

Adverse events that led to treatment discontinuation occurred in 4 of 36 subjects (11.1%) in the trabectedin group. The adverse events that led to treatment discontinuation were platelet count decreased (2 subjects, 5.6%); fatigue, rhabdomyolysis, febrile neutropenia, and blood ALP increased (1 subject each, 2.8%); and a causal relationship to the study drug could not be ruled out for the following events: platelet count decreased (2 subjects); rhabdomyolysis, febrile neutropenia, and blood ALP increased (1 subject each).

4.(iv).(3) Japanese phase II study (Study 10045040)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 27 of 28 subjects (96.4%). The table below shows adverse events with an incidence of ≥20%.

Adverse events with an incidence of ≥20%

System Organ Class (SOC) Preferred term (MedDRA/J ver.16.1)	Number of subjects (%) 28 subjects	
	All Grades	≥ Grade 3
Adverse events total	28 (100)	26 (92.9)
Blood and lymphatic system disorders		
Anaemia	7 (25.0)	7 (25.0)
Gastrointestinal disorders		
Constipation	17 (60.7)	1 (3.6)
Nausea	26 (92.9)	1 (3.6)
Vomiting	11 (39.3)	0
General disorders and administration site conditions		
Malaise	18 (64.3)	0
Pyrexia	6 (21.4)	0
Investigations		
ALT increased	19 (67.9)	19 (67.9)
AST increased	18 (64.3)	15 (53.6)
GGT increased	12 (42.9)	12 (42.9)
Lymphocyte count decreased	6 (21.4)	6 (21.4)
Neutrophil count decreased	26 (92.9)	24 (85.7)
Platelet count decreased	11 (39.3)	6 (21.4)
White blood cell count decreased	19 (67.9)	19 (67.9)
Blood ALP increased	6 (21.4)	0
Metabolism and nutrition disorders		
Decreased appetite	20 (71.4)	5 (17.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase

Serious adverse events occurred in 9 of 28 subjects (32.1%). The serious adverse events were as follows: febrile neutropenia and anaemia (3 subjects each, 10.7%); disease progression and decreased appetite (2 subjects each, 7.1%); tumour haemorrhage, pleural effusion, dehydration, ALT increased, AST increased, and nausea (1 subject each, 3.6%). Among these events, a causal relationship to the study drug could not be ruled out for the following events: febrile neutropenia (3 subjects), anaemia and decreased appetite (2 subjects each), tumour haemorrhage, dehydration, ALT increased, AST increased, and nausea (1 subject each).

Adverse events that led to treatment discontinuation occurred in 2 of 28 subjects (7.1%). The adverse events that led to treatment discontinuation were decreased appetite and nausea (2 subjects each, 7.1%), AST increased, ALT increased, malaise, and vomiting (1 subject each, 3.6%), and a causal relationship to the study drug could not be ruled for any of these events.

4.(iv).(4) Foreign phase I study (Study ET-A-002-95)

Adverse events occurred in all subjects; and adverse events for which a causal relationship to the study drug could not be ruled out were reported in 1 of 3 subjects (33.3%) in the 0.05 mg/m^2 group, 2 of 3 subjects (66.7%) in the 0.1 mg/m^2 group, 1 of 3 subjects (33.3%) in the 0.2 mg/m^2 group, 2 of 3 subjects (66.7%) in the 0.4 mg/m^2 group, 3 of 3 subjects (100%) in the 0.6 mg/m^2 group, 3 of 3 subjects (100%) in the 0.9 mg/m^2 group, 5 of 5 subjects (100%) in the 1.2 mg/m^2 group, 25 of 25 subjects (100%) in the 1.5 mg/m^2 group, and 4 of 4 subjects (100%) in the 1.8 mg/m^2 group.

Adverse events that occurred in ≥3 subjects were as follows: in the 0.05 mg/m^2 group, anaemia in 3 subjects (100%); in the 0.2 mg/m^2 group, anaemia in 3 subjects (100%); in the 0.4 mg/m^2 group, anaemia in 3 subjects (100%); in the 0.6 mg/ m^2 group, nausea in 3 subjects (100%); in the 0.9 mg/m^2 group, nausea, ALT increased, and AST increased in 3 subjects each (100%); in the 1.2 mg/m^2 group, anaemia, leukopenia, vomiting, ALT increased, and AST increased in 5 subjects each (100%), neutropenia in 4 subjects (80.0%), and nausea and blood bilirubin increased in 3 subjects each (60.0%); in the 1.5 mg/m^2 group, anaemia, ALT increased, and AST increased in 25 subjects each (100%), leukopenia in 22 subjects (88.0%), neutropenia and nausea in 19 subjects each (76.0%), vomiting in 16 subjects (64.0%), thrombocytopenia in 15 subjects (60.0%), asthenia and blood bilirubin increased in 13 subjects each (52.0%), pyrexia in 9 subjects (36.0%), blood creatinine increased in 6 subjects (24.0%), and abdominal pain, diarrhoea, and dyspnoea in 5 subjects each (20.0%); in the 1.8 mg/m^2 group, anaemia, leukopenia, neutropenia, nausea, vomiting, ALT increased, and AST increased in 4 subjects each (100%), and thrombocytopenia, asthenia, and blood bilirubin increased in 3 subjects each (75.0%). Among these, ≥ Grade 3 events were anaemia in the 0.05, 0.2, and 0.4 mg/m^2 groups (1 subject each), ALT increased and AST increased (1 subject each) in the 0.9 mg/m^2 group, anaemia (3 subjects), ALT increased and AST increased (2 subjects each), and vomiting (1 subject) in the 1.2 mg/m^2 group, AST increased (16 subjects), neutropenia and ALT increased (13 subjects each), leukopenia (12 subjects), blood bilirubin increased (9 subjects), anaemia and thrombocytopenia (7 subjects each), nausea and vomiting (4 subjects each), asthenia (3 subjects), and abdominal pain, blood creatinine increased, and dyspnoea (1 subject each) in the 1.5 mg/m^2 group, and leukopenia and neutropenia (4 subjects each), ALT increased and AST increased (3 subjects each), anaemia and thrombocytopenia (2 subjects each), and blood bilirubin increased (1 subject) in the 1.8 mg/m^2 group.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 0.05, 0.1, 0.2, 0.4, and 0.9 mg/m^2 groups; 4 of 5 subjects (80.0%) in the 1.2 mg/m^2 group, 12 of 25 subjects (48.0%) in the 1.5 mg/m^2 group, and 1 of 4 subjects (25.0%) in the 1.8 mg/m^2 group. Serious adverse events that occurred in ≥2 subjects in each group were pyrexia (5 subjects, 20.0%), thrombocytopenia and neutropenia (3 subjects each, 12.0%), and dyspnoea, headache, nausea, chills, and disease progression (2 subjects each, 8.0%) in the 1.5 mg/m^2 group; and thrombocytopenia and neutropenia (2 subjects each, 50.0%) in the 1.8 mg/m^2 group. Among these, a causal relationship to the study drug could not be ruled out for thrombocytopenia and neutropenia (3 subjects each), and pyrexia (1 subject) in the 1.5 mg/m^2 group, and thrombocytopenia and neutropenia (2 subjects each) in the1.8 mg/m^2 group.

Adverse events that led to treatment discontinuation occurred in 1 of 25 subjects (4.0%) in the 1.5 mg/m^2 group. The adverse events that led to treatment discontinuation were thrombocytopenia and neutropenia (1 subject each, 4.0%), and a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(5) Foreign phase I study (Study ET-A-006-00)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in the following subjects: in patients with mild hepatic dysfunction, 3 of 3 subjects (100%) in the 1.1 mg/m^2 group, and 13 of 13 subjects (100%) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, 3 of 4 subjects (75.0%) in the 0.9 mg/m^2 group, 3 of 3 subjects (100%) in the 1.1 mg/m^2 group, and 3 of 5 subjects (60.0%) in the 1.3 mg/m^2 group; in patients with severe hepatic dysfunction, 3 of 3 subjects (100%) in the 0.75 mg/m^2 group, and 1 of 2 subjects (50.0%) in the 0.9 mg/m^2 group.

Adverse events with an incidence of ≥60% in each group were as follows: in patients with mild hepatic dysfunction, fatigue and tumour pain (3 subjects each, 100%), and queasy, anorexia, peripheral sensory neuropathy, cough, and dyspnoea (2 subjects each, 66.7%) in the 1.1 mg/m^2 group, and fatigue (12 subjects, 92.3%) and queasy (11 subjects, 84.6%) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, tumor pain (4 subjects, 100%), and constipation and fatigue (3 subjects each, 75.0%) in the 0.9 mg/m^2 group, queasy, fatigue, anorexia, and peripheral sensory neuropathy (3 subjects each, 100%), and diarrhoea and vomiting (2 subjects each, 66.7%) in the 1.1 mg/m^2 group, and fatigue (5 subjects, 100%), abdominal pain upper, and anorexia (3 subjects each, 60.0%) in the 1.3 mg/m^2 group; in patients with severe hepatic dysfunction, fatigue and anorexia (3 subjects each, 100%), and constipation, queasy, vomiting, and myalgia (2 subjects each, 66.7%) in the 0.75 mg/m^2 group, and queasy, fatigue, and anorexia (2 subjects each, 100%) in the 0.9 mg/m^2 group. Among these, ≥ Grade 3 events were in patients with mild hepatic dysfunction, fatigue (1 subject, 33.3%) in the 1.1mg/m^2 group, and fatigue (2 subjects, 15.4%) and queasy (1 subject, 7.7%) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, constipation (1 subject, 25.0%) in the 0.9 mg/m^2 group, and fatigue (2 subjects, 40.0%) and anorexia (1 subject, 20.0%) in the 1.3 mg/m^2 group; in patients with severe hepatic dysfunction, queasy and vomiting (1 subject each, 33.3%) in the 0.75 mg/m^2 group, and fatigue (1 subject, 50.0%) in the 0.9 mg/m^2 group.

Serious adverse events occurred, in patients with mild hepatic dysfunction, in 6 of 13 subjects (46.2%) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, in 1 of 4 subjects (25.0%) in the 0.9 mg/m^2 group, and in 2 of 5 subjects (40.0%) in the 1.3 mg/m^2 group; and in patients with severe hepatic dysfunction, 2 of 3 subjects (66.7%) in the 0.75 mg/m^2 group, and 1 of 2 subjects (50.0%) in the 0.9 mg/m^2 group. The serious adverse events were as follows: in patients with mild hepatic dysfunction, cardiac tamponade, dyspnoea, cardiac hypertrophy, hypotension, confusional state, headache, queasy, vomiting, myalgia, anxiety, atelectasis, hydropneumothorax, febrile neutropenia, thrombocytopenia,

renal failure, cardiac failure congestive, asthenia, disease progression, GGT increased, intestinal obstruction, haemorrhoids, proctalgia, constipation, subileus, and abdominal pain (1 subject each, 7.7%) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, intestinal obstruction, and disease progression (1subject each, 25.0%) in the 0.9 mg/m^2 group, and upper gastrointestinal haemorrhage, anaemia, neutropenia, and thrombocytopenia (1 subject each, 20.0%) in the 1.3 mg/m^2 group; and in patients with severe hepatic dysfunction, adenocarcinoma, blood CPK increased, pyrexia, and hypercalcaemia (1 subject each, 33.3%) in the 0.75 mg/m^2 group, and Escherichia bacteraemia (1 subject, 50.0%) in the 0.9 mg/m^2 group. Among these, a causal relationship to the study drug could not be ruled out for the following: in patients with mild hepatic dysfunction, renal failure, GGT increased, febrile neutropenia, and thrombocytopenia (1 subject each) in the 1.3 mg/m^2 group; in patients with moderate hepatic dysfunction, neutropenia and thrombocytopenia (1 subject each) in the 1.3 mg/m^2 group; in patients with severe hepatic dysfunction, blood CPK increased (1 subject) in the 0.75 mg/m^2 group, and Escherichia bacteraemia (1 subject) in the 0.9 mg/m^2 group.

An adverse event that led to treatment discontinuation occurred in 1 subject (50.0%) with severe hepatic dysfunction in the 0.9 mg/m^2 group. The adverse event that led to treatment discontinuation was exacerbated hepatic dysfunction with transaminases increased, and a causal relationship to the study drug could not be ruled out.

4.(iv).(6) Foreign phase I study (Study ET-A-013-01)

Adverse events occurred in all subjects; and a causal relationship to the study drug could not be ruled out in 7 of 8 subjects (87.5%) in Cycle 1 (1.1 mg/m^2 group) and 8 of 8 subjects (100%) in Cycle 2 (6 subjects in the 1.3 mg/m^2 group, and 2 subjects in the 1.5 mg/m^2 group).

Adverse events with an incidence of ≥30% in each group were as follows: nausea (6 subjects, 75.0%), fatigue (4 subjects, 50.0%), and constipation, vomiting, and dyspnoea (3 subjects each, 37.5%) in Cycle 1; fatigue and dyspnoea (5 subjects each, 62.5%), and nausea (4 subjects, 50.0%) in Cycle 2. Among these, ≥ Grade 3 events were dyspnoea (1 subject, 12.5%) in Cycle 1, dyspnoea (4 subjects, 50.0%), and fatigue (2 subjects, 25.0%) in Cycle 2.

Serious adverse events occurred in 6 of 8 subjects (75.0%). The serious adverse events that occurred were dyspnoea (2 subjects, 25.0%), and catheter related complications, euthanasia, ileus, dehydration, disease progression, pyrexia, anaemia, neutropenia, Escherichia bacteraemia, angina pectoris, and dyspnoea exacerbated (1 subject each, 12.5%), and a causal relationship to the study drug could not be ruled out for neutropenia and Escherichia bacteraemia (1 subject each).

Adverse events that led to treatment discontinuation occurred in 2 of 8 subjects (25.0%). The adverse events that led to treatment discontinuation were dyspnoea (2 subjects, 25.0%), and a causal relationship to the study drug was ruled out for both events.

4.(iv).(7) Foreign phase I/II study (Study ET743-OVC-1001)

Adverse events occurred in 74 of 75 subjects (98.7%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 70 of 75 subjects (93.3%). The table below shows the adverse events with an incidence of ≥20%.

Adverse events with an incidence of ≥20%

System Organ Class (SOC) Preferred term (MedDRA/J ver.11.1)	Number of subjects (%) 75 subjects	
	All Grades	≥ Grade 3
Adverse events total	74 (98.7)	59 (78.7)
Gastrointestinal disorders		
Nausea	39 (52.0)	4 (5.3)
Vomiting	33 (44.0)	5 (6.7)
General disorders and administration site conditions		
Asthenia	27 (36.0)	5 (6.7)
Fatigue	17 (22.7)	1 (1.3)
Blood and lymphatic system disorders		
Neutropenia	32 (42.7)	26 (34.7)
Anaemia	24 (32.0)	12 (16.0)
Thrombocytopenia	16 (21.3)	10 (13.3)
Hepatobiliary disorders		
Hepatic function abnormal	35 (46.7)	25 (33.3)
Metabolism and nutrition disorders		
Anorexia	18 (24.0)	2 (2.7)

Serious adverse events occurred in 33 of 75 subjects (44.0%). Serious adverse events that occurred in ≥2 subjects were neutropenia (6 subjects, 8.0%), febrile neutropenia (5 subjects, 6.7%), thrombocytopenia, asthenia, pyrexia, and vomiting (4 subjects each, 5.3%), rhabdomyolysis (3 subjects, 4.0%), and anaemia, nausea, renal failure, hepatic function abnormal, and decreased appetite (2 subjects each, 2.7%). A causal relationship to the study drug could not be ruled out for the following events: neutropenia (6 subjects), febrile neutropenia (5 subjects), thrombocytopenia (4 subjects), rhabdomyolysis and vomiting (3 subjects each), nausea, hepatic function abnormal, decreased appetite, asthenia, and renal failure (2 subjects each), and pyrexia and anaemia (1 subject each).

Adverse events that led to treatment discontinuation occurred in 6 of 75 subjects (8.0%). The adverse events that led to treatment discontinuation were neutropenia, rhabdomyolysis, and hepatic function abnormal (2 subjects each, 2.7%), and thrombocytopenia, leukopenia, hyperbilirubinaemia, and febrile neutropenia (1 subject each, 1.3%), and a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(8) Foreign phase I/II study (Study ET743-OVC-1002)

Adverse events occurred in 5 of 5 subjects (100%) in treatment sequence 1 (co-administration of trabectedin with RFP, followed by trabectedin monotherapy) and 6 of 6 subjects (100%) in treatment sequence 2 (trabectedin monotherapy followed by co-administration of trabectedin with RFP), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 of

5 subjects (80.0%) and 6 of 6 subjects (100%), respectively. The table below shows the adverse events with an incidence of ≥30% in at least 1 group.

Adverse events with an incidence of ≥ 30% in at least 1 group

System Organ Class (SOC) Preferred term (MedDRA/J ver15.0)	Number of subjects (%)			
	Treatment sequence 1 5 subjects		Treatment sequence 2 6 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	5 (100)	5 (100)	6 (100)	4 (66.7)
Blood and lymphatic system disorders				
Anaemia	2 (40.0)	1 (20.0)	1 (16.7)	1 (16.7)
Leukopenia	3 (60.0)	3 (60.0)	1 (16.7)	1 (16.7)
Neutropenia	2 (40.0)	1 (20.0)	2 (33.3)	2 (33.3)
Thrombocytopenia	2 (40.0)	2 (40.0)	2 (33.3)	2 (33.3)
Gastrointestinal disorders				
Diarrhoea	0	0	3 (50.0)	0
Dry mouth	0	0	2 (33.3)	0
Nausea	5 (100)	0	5 (83.3)	1 (16.7)
Vomiting	3 (60.0)	0	3 (50.0)	2 (33.3)
General disorders and administration site conditions				
Fatigue	2 (40.0)	0	3 (50.0)	0
Pyrexia	0	0	3 (50.0)	0
Hepatobiliary disorders				
Hepatic function abnormal	3 (60.0)	2 (40.0)	3 (50.0)	3 (50.0)
Metabolism and nutrition disorders				
Decreased appetite	2 (40.0)	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders				
Back pain	2 (40.0)	1 (20.0)	1 (16.7)	0
Nervous system disorders				
Dizziness	1 (20.0)	0	2 (33.3)	0
Headache	0	0	3 (50.0)	0

Serious adverse events occurred in 2 of 5 subjects (40.0%) in treatment sequence 1; and 2 of 6 subjects (33.3%) in treatment sequence 2. The serious adverse events occurred were ascites and back pain (1 subject each, 20.0%) in treatment sequence 1, and hepatic function abnormal and pyelonephritis (1 subject each, 16.7%). A causal relationship to the study drug could not be ruled out for hepatic function abnormal (1 subject) in treatment sequence 2.

Adverse events that led to treatment discontinuation occurred in 1 of 6 subjects (16.7%) in treatment sequence 2. The adverse event that led to treatment discontinuation was neutropenia (1 subject, 16.7%), and a causal relationship to the study drug could not be ruled out.

4.(iv).(9) Foreign phase I/II study (Study ET743-OVC-1003)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in all subjects.

Adverse events that occurred in ≥3 subjects in each group were as follows: in Part A (0.2 mg/m^2 of trabectedin co-administered with KCZ, followed by monotherapy of 1.3 mg/m^2 of trabectedin), nausea

and fatigue (3 subjects each, 75.0%); in treatment sequence 1 of Part B (0.58 mg/m^2 of trabectedin co-administered with KCZ, followed by monotherapy of 1.3 mg/m^2 of trabectedin), nausea and vomiting (4 subjects each, 100%), and anaemia and decreased appetite (3 subjects each, 75.0%); in treatment sequence 2 of Part B (monotherapy of 1.3 mg/m^2 of trabectedin, followed by 0.58 mg/m^2 of trabectedin co-administered with KCZ), anaemia, neutropenia, thrombocytopenia, constipation, diarrhoea, asthenia, pyrexia, hypomagnesaemia, and hepatic function abnormal (3 subjects each, 75.0%). Among these, ≥ Grade 3 events were anaemia (1 subject, 25.0%) in the treatment sequence 1; anaemia and thrombocytopenia (2 subjects each, 50.0%), and neutropenia and hepatic function abnormal (1 subject each, 25.0%) in the treatment sequence 2 in Part B.

Serious adverse events occurred in 3 of 4 subjects (75.0%) in Part A, 2 of 4 subjects (50.0%) in treatment sequence 1 of Part B, and 3 of 4 subjects (75.0%) in treatment sequence 2 of Part B. The serious adverse events occurred in Part A were febrile neutropenia, abdominal pain, neutropenia, pain in extremity, pyrexia, and hepatic function abnormal (1 subject each, 25.0%); in Part B, renal impairment, asthenia, euthanasia, and neutropenia (1 subject each, 25.0%) in the treatment sequence 1, and thrombocytopenia, pyrexia, and dehydration (2 subjects each, 50.0%), and acute coronary syndrome, neutropenia, diarrhoea, musculoskeletal pain, haematuria, cystitis, and febrile neutropenia (1 subject each, 25.0%) in the treatment sequence 2. Among these, a causal relationship to the study drug could not be ruled out for the following events: in Part A, febrile neutropenia, abdominal pain, neutropenia, pyrexia, and hepatic function abnormal (1 subject each); in Part B, asthenia and neutropenia (1 subject each) in the treatment sequence 1, and thrombocytopenia (2 subjects), neutropenia, and febrile neutropenia (1 subject each) in the treatment sequence 2.

There were no adverse events that led to treatment discontinuation.

4.(iv).(10) Foreign phase II study (Study ET-743-STS-201)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 117 of 130 subjects (90.0%) in the QW-3h group, 122 of 130 subjects (93.8%) in the Q3W-24h group. The table below shows the adverse events with an incidence of ≥30% in at least 1 group.

Adverse events with an incidence of ≥30% in at least 1 group

System Organ Class (SOC) Preferred term (MedDRA/J ver8.0)	Number of subjects (%)			
	QW-3h 130 subjects		Q3W-24h 130 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	130 (100)	93 (71.5)	130 (100)	111 (85.4)
Blood and lymphatic system disorders				
Anaemia	45 (34.6)	8 (6.2)	42 (32.3)	2 (1.5)
Neutropenia	48 (36.9)	31 (23.8)	75 (57.7)	56 (43.1)
Gastrointestinal disorders				
Constipation	47 (36.2)	2 (1.5)	45 (34.6)	0
Nausea	77 (59.2)	5 (3.8)	98 (75.4)	7 (5.4)
Vomiting	37 (28.5)	4 (3.1)	57 (43.8)	7 (5.4)
General disorders and administration site conditions				
Fatigue	73 (56.2)	9 (6.9)	76 (58.5)	8 (6.2)
Investigations				
ALT increased	56 (43.1)	21 (16.2)	72 (55.4)	52 (40.0)
AST increased	43 (33.1)	13 (10.0)	63 (48.5)	30 (23.1)
Blood ALP increased	40 (30.8)	3 (2.3)	40 (30.8)	3 (2.3)
Nervous system disorders				
Headache	39 (30.0)	2 (1.5)	37 (28.5)	1 (0.8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase

Serious adverse events occurred in 51 of 130 subjects (39.2%) in the QW-3h group, and 58 of 130 subjects (44.6%) in the Q3W-24h group. Serious adverse events that occurred in ≥2 subjects in a group were leiomyosarcoma (7 subjects, 5.4%), pyrexia (6 subjects, 4.6%), pain (4 subjects, 3.1%), small intestinal obstruction, liposarcoma metastatic, pulmonary embolism, sepsis, cardiac failure congestive, dehydration, leiomyosarcoma metastatic, pneumonia, vomiting, abdominal pain, and nausea (3 subjects each, 2.3%), and anaemia, spinal cord compression, intestinal obstruction, liposarcoma, surgery, malignant neoplasm progression, dyspnoea, and myocardial infarction (2 subjects each, 1.5%) in the QW-3h group; pneumonia (7 subjects, 5.4%), abdominal pain and vomiting (6 subjects each, 4.6%), sarcoma (5 subjects, 3.8%), small intestinal obstruction, pleural effusion, malignant neoplasm progression, pyrexia, and deep vein thrombosis (4 subjects each, 3.1%), nausea, liposarcoma metastatic, leiomyosarcoma, pulmonary embolism, subclavian vein thrombosis, hypotension, disease progression, and pyopneumothorax (3 subjects each, 2.3%), and catheter related infection, intestinal obstruction, sepsis, tumour haemorrhage, dyspnoea, leiomyosarcoma metastatic, atrial fibrillation, thrombocytopenia, pulmonary hypertension, tachycardia, renal failure acute, back pain, and anaemia (2 subjects each, 1.5%) in the Q3W-24h group. Among these, a causal relationship to the study drug could not be ruled out for the following events: pneumonia, vomiting, and nausea (2 subjects each), and sepsis, cardiac failure congestive, dehydration, leiomyosarcoma metastatic, abdominal pain, and anaemia (1 subject each) in the QW-3h group, vomiting (4 subjects), nausea and deep vein thrombosis (3 subjects each), abdominal pain and thrombocytopenia (2 subjects each), and pneumonia, small intestinal obstruction, pulmonary embolism, hypotension, disease progression, atrial fibrillation, pulmonary hypertension, renal failure acute, and anaemia (1 subject each) in the Q3W-24h group.

Adverse events that led to treatment discontinuation occurred in 13 of 130 subjects (10.0%) in the QW-3h group, and 13 of 130 subjects (10.0%) in the Q3W-24h group. Adverse events that led to treatment discontinuation in ≥2 subjects were ALP increased (2 subjects, 1.5%) in the QW-3h group, and neutropenia (3 subjects, 2.3%), and ALP increased (2 subjects, 1.5%) in the Q3W-24h group. Among these, a causal relationship to the study drug could not be ruled out for ALP increased (1 subject, 0.8%) in the QW-3h group, and neutropenia (3 subjects, 2.3%) and ALP increased (2 subjects, 1.5%) in the Q3W-24h group.

4.(iv).(11) Foreign phase II study (Study ET-B-005-98)

Adverse events occurred in 95 of 99 subjects (96.0%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 87 of 99 subjects (87.9%). The table below shows adverse events with an incidence of ≥30%.

Adverse events with an incidence of ≥30%

System Organ Class (SOC) Preferred term (MedDRA/J ver5.0)	Number of subjects (%) 99 subjects	
	All Grades	≥ Grade 3
Adverse events total	95 (96.0)	52 (52.5)
Gastrointestinal disorders		
Constipation	35 (35.4)	2 (2.0)
Nausea	68 (68.7)	8 (8.1)
Vomiting	45 (45.5)	9 (9.1)
General disorders and administration site conditions		
Fatigue	78 (78.8)	15 (15.2)
Metabolism and nutrition disorders		
Anorexia	33 (33.3)	5 (5.1)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	32 (32.3)	12 (12.1)

Serious adverse events occurred in 42 of 99 subjects (42.4%). Serious adverse events that occurred in ≥2 subjects were disease progression (9 subjects, 9.1%), vomiting (7 subjects, 7.1%), thrombocytopenia (6 subjects, 6.1%), nausea (5 subjects, 5.1%), febrile neutropenia (4 subjects, 4.0%), sepsis, condition aggravated, pancytopenia, anorexia, and lower respiratory tract infection (3 subjects each, 3.0%), and raised liver enzymes, cardiac failure, renal failure acute, dehydration, neutropenia, abdominal pain, cardiogenic shock, renal failure, blood creatinine increased, dyspnoea, pyrexia, infection, chest pain, and fatigue (2 subjects, 2.0%). Among these, a causal relationship to the study drug could not be ruled out for the following events: thrombocytopenia and vomiting (6 subjects each), nausea and febrile neutropenia (4 subjects each), disease progression, anorexia, and pancytopenia (3 subjects each), cardiogenic shock, dehydration, neutropenia, renal failure, sepsis, blood creatinine increased, pyrexia, and fatigue (2 subjects each), and abdominal pain, condition aggravated, raised liver enzymes, chest pain, cardiac failure, and renal failure acute (1 subject each).

Adverse events that led to treatment discontinuation occurred in 12 of 99 subjects (12.1%). The adverse events that led to treatment discontinuation were renal failure and neutropenia (3 subjects each, 3.0%),

liver enzyme abnormal (2 subjects, 2.0%), and haemorrhage, pulmonary oedema, neutropenic sepsis, confusion, febrile neutropenia, ALP increased, and thrombocytopenia (1 subject each, 1.0%), and a causal relationship to the study drug was unknown.

4.(iv).(12) Foreign phase II study (Study ET-B-008-98)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 25 of 26 subjects (96.2%) in Group 1, and 26 of 28 subjects (92.9%) in Group 2. The table below shows adverse events with an incidence of ≥30% in at least 1 group.

Adverse events with an incidence of ≥30% in at least 1 group.

System Organ Class (SOC) Preferred term (MedDRA/J ver.5.0)	Number of subjects (%)			
	Group 1 26 subjects		Group 2 28 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	26 (100)	9 (34.6)	28 (100)	12 (42.9)
Gastrointestinal disorders				
Constipation	13 (50.0)	0	7 (25.0)	0
Nausea	22 (84.6)	2 (7.7)	23 (82.1)	2 (7.1)
Vomiting	13 (50.0)	3 (11.5)	20 (71.4)	2 (7.1)
General disorders and administration site conditions				
Fatigue	20 (76.9)	5 (19.2)	27 (96.4)	4 (14.3)
Pyrexia	6 (23.1)	1 (3.8)	10 (35.7)	0
Nervous system disorders				
Headache	8 (30.8)	0	7 (25.0)	1 (3.6)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	7 (26.9)	1 (3.8)	13 (46.4)	3 (10.7)

Serious adverse events occurred in 8 of 26 subjects (30.8%) in Group 1, and 7 of 28 subjects (25.0%) in Group 2. Serious adverse events occurred in ≥2 subjects in a group were febrile neutropenia and thrombocytopenia (3 subjects each, 11.5%), and disease progression and rhabdomyolysis (2 subjects each, 7.7%) in Group 1, and pyrexia (3 subjects, 10.7%), and vomiting and renal failure (2 subjects each, 7.1%) in Group 2. Among these, a causal relationship to the study drug could not be ruled out for the following events: febrile neutropenia and thrombocytopenia (3 subjects each), and rhabdomyolysis (2 subjects) in Group 1, and vomiting and renal failure (1 subject each) in Group 2.

Adverse events that led to treatment discontinuation occurred in 4 of 26 subjects (15.4%) in Group 1, and 2 of 28 subjects (7.1%) in Group 2. The adverse events that led to treatment discontinuation were fatigue, cirrhosis, rhabdomyolysis, renal failure acute, febrile neutropenia, thrombocytopenia, and disease progression (1 subject each, 3.8%) in Group 1, and vomiting and disease progression (1 subject each, 3.6%) in Group 2, and a causal relationship to the study drug could not be ruled out for the following events: fatigue, cirrhosis, rhabdomyolysis, renal failure acute, febrile neutropenia, and thrombocytopenia (1 subject each) in Group 1, and vomiting (1 subject) in Group 2.

4.(iv).(13) Foreign phase II study (Study ET-B-010-99)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 8 of 8 subjects (100%) in the 1.65 mg/m^2 group, 25 of 25 subjects (100%) in the 1.5 mg/m^2 group, and 7 of 8 subjects (87.5%) in the 1.3 mg/m^2 group.

Adverse events with an incidence of ≥30% in a group were fatigue and pain (7 subjects each, 87.5%), anorexia and queasy (6 subjects each, 75.0%), vomiting (5 subjects, 62.5%), constipation (4 subjects, 50.0%), and pyrexia (3 subjects, 37.5%) in the 1.65 mg/m^2 group; fatigue (22 subjects, 88.0%), vomiting (16 subjects, 64.0%), pain (15 subjects, 60.0%), queasy and dyspnoea (13 subjects each, 52.0%), injection site reaction (12 subjects, 48.0%), constipation (9 subjects, 36.0%), and anorexia (8 subjects, 32.0%) in the 1.5 mg/m^2 group; and queasy (6 subjects, 75.0%), fatigue and vomiting (5 subjects each, 62.5%), pain (4 subjects, 50.0%), and anorexia and constipation (3 subjects each, 37.5%) in the 1.3 mg/m^2 group. Among these events, ≥ Grade 3 were vomiting (3 subjects, 37.5%) and pain (2 subjects, 25.0%) in the 1.65 mg/m^2 group, vomiting (7 subjects, 28.0%), fatigue (5 subjects, 20.0%), queasy and dyspnoea (4 subjects each, 16.0%), and anorexia and pain (1 subject each, 4.0%) in the 1.5 mg/m^2 group, and fatigue and vomiting (2 subjects each, 25.0%) in the 1.3 mg/m^2 group.

Serious adverse events occurred in 5 of 8 subjects (62.5%) in the 1.65 mg/m^2 group, 13 of 25 subjects (52.0%) in the 1.5 mg/m^2 group, and 4 of 8 subjects (50.0%) in the 1.3 mg/m^2 group. Serious adverse events that occurred in ≥2 subjects in a group were febrile neutropenia (5 subjects, 20.0%), vomiting, dyspnoea, renal failure, and fatigue (4 subjects each, 16.0%), and queasy, respiratory failure, pyrexia, and cardiac failure (2 subjects each, 8.0%) in the 1.5 mg/m^2 group. Among these, a causal relationship to the study drug could not be ruled out for the following events: febrile neutropenia (5 subjects), vomiting, renal failure, and fatigue (4 subjects each), queasy, pyrexia, and cardiac failure (2 subjects each), and respiratory failure (1 subject).

Adverse events that led to treatment discontinuation occurred in 3 of 25 subjects (12.0%) in the 1.5 mg/m^2 group, and 1 of 8 subjects (12.5%) in the 1.3 mg/m^2 group. The adverse events that led to treatment discontinuation were febrile neutropenia (3 subjects, 12.0%) in 1.5 mg/m^2 group and bilirubin increased (1 subject, 12.5%) in the 1.3 mg/m^2 group, and a causal relationship to the study drug could not be ruled out in any of these events.

4.(iv).(14) Foreign phase II study (Study ET-B-016-99)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 34 of 36 subjects (94.4%).

Adverse events with an incidence of ≥30% were fatigue (30 subjects, 83.3%), nausea (26 subjects, 72.2%), constipation (24 subjects, 66.7%), and other pain and dyspnoea (13 subjects each, 36.1%). Among these events, ≥ Grade 3 adverse events were nausea (5 subjects, 13.9%), fatigue (4 subjects, 11.1%), and other pain and dyspnoea (2 subjects each, 5.6%).

Serious adverse events occurred in 13 of 36 subjects (36.1%). The serious adverse events were pyrexia, nausea, and vomiting (2 subjects each, 5.6%), and blood culture positive, pulmonary embolism, vein disorder, systolic hypertension, anaemia, dehydration, hypoglycaemia, cardiac tamponade, chest discomfort, fluid overload, dyspnoea, pneumonia, productive cough, small intestinal obstruction, surgery, injection site infection, conduction disorder, and injection site thrombosis (1 subject each, 2.8%). Among these, a causal relationship to the study drug could not be ruled out for nausea and vomiting (2 subjects each), and pyrexia, dehydration, hypoglycaemia, dyspnoea, pneumonia, and injection site infection (1 subject each).

Adverse events that led to treatment discontinuation occurred in 2 of 36 subjects (5.6%). The adverse events that led to treatment discontinuation were fatigue (2 subjects, 5.6%), anorexia, abdominal distension, abdominal pain, nausea, vomiting, pyrexia, and weight decreased (1 subject each, 2.8%); and a causal relationship to the study drug could not be ruled out for fatigue (2 subjects), anorexia, nausea, vomiting, pyrexia, and weight decreased (1 subject each).

4.(iv).(15) Foreign phase II study (Study ET-B-017-99)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 31 of 36 subjects (86.1%).

Adverse events with an incidence of ≥30% were fatigue (26 subjects, 72.2%), nausea (22 subjects, 61.1%), constipation (19 subjects, 52.8%), pain and dyspnoea (12 subjects each, 33.3%). Among these events, ≥ Grade 3 adverse events were nausea (3 subjects, 8.3%), fatigue and dyspnoea (2 subjects each, 5.6%), and constipation and pain (1 subject each, 2.8%).

Serious adverse events occurred in 12 of 36 subjects (33.3%). The serious adverse events were dyspnoea (4 subjects, 11.1%), disease progression (3 subjects, 8.3%), deep vein thrombosis and febrile neutropenia (2 subjects each, 5.6%), and catheter-related complication, pleural effusion, pulmonary embolism, abdominal pain, superior vena caval occlusion, pyrexia, cough, thrombosis, nausea, vomiting, constipation, myeloid leukaemia, headache, malaise, renal failure, hepatic function abnormal, and axillary mass (1 subject each, 2.8%). Among these events, a causal relationship to the study drug could not be ruled out for febrile neutropenia (2 subjects), abdominal pain, nausea, vomiting, and constipation (1 subject each).

Adverse events that led to treatment discontinuation occurred in 2 of 36 subjects (5.6%). The adverse events that led to treatment discontinuation were acute myeloid leukaemia and fatigue (1 subject each, 2.8%); and a causal relationship to the study drug could not be ruled out for fatigue (1 subject).

4.(iv).(16) Foreign phase II study (Study ET-B-022-00)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 62 of 68 subjects (91.2%).

Adverse events with an incidence of ≥30% were fatigue (57 subjects, 83.8%), queasy (40 subjects, 58.8%), constipation (30 subjects, 44.1%), tumor pain (27 subjects, 39.7%), vomiting (24 subjects, 35.3%), dyspnoea (23 subjects, 33.8%), and anorexia (22 subjects, 32.4%). Among these events, ≥ Grade 3 adverse events were fatigue and dyspnoea (5 subjects each, 7.4%), queasy (3 subjects, 4.4%), vomiting and tumor pain (2 subjects each, 2.9%), and constipation and anorexia (1 subject each, 1.5%).

Serious adverse events occurred in 21 of 68 subjects (30.9%). Serious adverse events that occurred in ≥2 subjects were pyrexia (5 subjects, 7.4%), febrile neutropenia (4 subjects, 5.9%), dyspnoea (3 subjects, 4.4%), and neutropenia (2 subjects, 2.9%). Among these events, a causal relationship to the study drug could not be ruled out for febrile neutropenia (4 subjects), pyrexia (3 subjects), and neutropenia (2 subjects).

Adverse events that led to treatment discontinuation occurred in 3 of 68 subjects (4.4%). The serious adverse events were thrombocytopenia (3 subjects, 4.4%), neutropenia (2 subjects, 2.9%), and anaemia (1 subject, 1.5%); and a causal relationship to the study drug could not be ruled out for any of these events.

4.(iv).(17) Foreign phase II study (Study ET-B-023-00)

Adverse events occurred in 64 of 75 subjects (85.3%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 60 of 75 subjects (80.0%).

Adverse events with an incidence of ≥30% were fatigue (46 subjects, 61.3%), queasy (39 subjects, 52.0%), and vomiting (26 subjects, 34.7%). Among these events, ≥ Grade 3 adverse events were fatigue (5 subjects, 6.7%), vomiting (4 subjects, 5.3%), and queasy (3 subjects, 4.0%).

Serious adverse events occurred in 17 of 75 subjects (22.7%). Serious adverse events that occurred in ≥2 subjects were thrombocytopenia (4 subjects, 5.3%), febrile neutropenia (3 subjects, 4.0%), queasy, vomiting, hepatic enzyme increased, cardiac failure, blood creatinine increased, asthenia, and neutropenia (2 subjects each, 2.7%). A causal relationship to the study drug could not be ruled out for the following events: thrombocytopenia (4 subjects), febrile neutropenia (3 subjects), queasy, vomiting, hepatic enzyme increased, cardiac failure, blood creatinine increased, asthenia, and neutropenia (2 subjects each).

Adverse events that led to treatment discontinuation occurred in 14 of 75 subjects (18.7%). The adverse events that led to treatment discontinuation were thrombocytopenia (4 subjects, 5.3%), neutropenia and hepatotoxicity (2 subjects each, 2.7%), and pulmonary oedema, meningitis, febrile neutropenia, ALT

increased, anaemia, fatigue, blood creatinine increased, cardiac failure, and dyspepsia (1 subject each, 1.3%). A causal relationship to the study drug could not be ruled out for the following events: thrombocytopenia (4 subjects), neutropenia and hepatotoxicity (2 subjects each), and febrile neutropenia, ALT increased, anaemia, fatigue, blood creatinine increased, cardiac failure, and dyspepsia (1 subject each).

4.(iv).(18) Foreign phase II study (Study ET-B-028-06)

Adverse events occurred in 28 of 29 subjects (96.6%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 28 of 29 subjects (96.6%).

Adverse events with an incidence of ≥20% were nausea (22 subjects, 75.9%), fatigue (19 subjects, 65.5%), vomiting and pyrexia (8 subjects, 27.6%), constipation (7 subjects, 24.1%), and cancer pain (6 subjects, 20.7%). Among these events, ≥ Grade 3 adverse events were fatigue (5 subjects, 17.2%), nausea and vomiting (2 subjects each, 6.9%), and constipation (1 subject, 3.4%).

Serious adverse events occurred in 6 of 29 subjects (20.7%). The serious adverse events were asthenia, nausea, ALT increased, AST increased, renal insufficiency, rhabdomyolysis, hepatic failure, colitis ischaemic, stomatitis, liver function test abnormal, and constipation (1 subject each, 3.4%). Among these, a causal relationship to the study drug could not be ruled out for the following events: asthenia, nausea, ALT increased, AST increased, renal insufficiency, rhabdomyolysis, hepatic failure, stomatitis, liver function test abnormal, and constipation (1 subject each).

Adverse events that led to treatment discontinuation occurred in 1 of 29 subjects (3.4%). The adverse event that led to treatment discontinuation was ALT increased (1 subject, 3.4%); and a causal relationship to the study drug could not be ruled out.

4.(iv).(19) Foreign phase III study (Study ET-C-002-07)

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out in 55 of 61 subjects (90.2%) in the trabectedin group, and 52 of 57 subjects (91.2%) in the DOX group. The table below shows the adverse events that occurred with an incidence of ≥20% in at least 1 group.

Adverse events that occurred with an incidence of ≥20% in at least 1 group

System Organ Class (SOC) Preferred term (MedDRA/J ver11.0)	Number of subjects (%)			
	Trabectedin 61 subjects		DOX 57 subjects	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Adverse events total	61 (100)	42 (68.9)	57 (100)	28 (49.1)
Gastrointestinal disorders				
Abdominal pain	15 (24.6)	1 (1.6)	12 (21.1)	2 (3.5)
Constipation	26 (42.6)	1 (1.6)	16 (28.1)	0
Diarrhoea	14 (23.0)	0	15 (26.3)	1 (1.8)
Nausea	47 (77.0)	1 (1.6)	39 (68.4)	0
Vomiting	28 (45.9)	1 (1.6)	16 (28.1)	0
General disorders and administration site conditions				
Fatigue	44 (72.1)	5 (8.2)	43 (75.4)	1 (1.8)
Mucosal inflammation	4 (6.6)	1 (1.6)	15 (26.3)	4 (7.0)
Oedema peripheral	18 (29.5)	0	5 (8.8)	0
Pyrexia	13 (21.3)	0	12 (21.1)	0
Metabolism and nutrition disorders				
Anorexia	20 (32.8)	2 (3.3)	15 (26.3)	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				
Tumor pain	35 (57.4)	5 (8.2)	32 (56.1)	2 (3.5)
Nervous system disorders				
Headache	13 (21.3)	0	14 (24.6)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	13 (21.3)	1 (1.6)	6 (10.5)	0
Skin and subcutaneous tissue disorders				
Alopecia	2 (3.3)	0	25 (43.9)	0

Serious adverse events occurred in 24 of 61 subjects (39.3%) in the trabectedin group, and 16 of 57 subjects (28.1%) in the DOX group. Serious adverse events that occurred in ≥2 subjects in a group were catheter-related infection (4 subjects, 6.6%), pyrexia, injection site extravasation, and device-related infection (3 subjects each, 4.9%), and anaemia, neutropenia, thrombocytopenia, vomiting, pain, and deep vein thrombosis (2 subjects each, 3.3%) in the trabectedin group; and febrile neutropenia (7 subjects, 12.2%), abdominal pain (3 subjects, 5.3%), and neutropenia, pyrexia, pneumonia, and pulmonary embolism (2 subjects each, 3.5%) in the DOX group. A causal relationship to the study drug could not be ruled out for the following events: injection site extravasation (3 subjects), anaemia, neutropenia, thrombocytopenia, and vomiting (2 subjects each), and pyrexia (1 subject) in the trabectedin group; and febrile neutropenia (7 subjects), neutropenia (2 subjects), and abdominal pain, pyrexia, and pneumonia (1 subject each) in the DOX group.

As for adverse events that led to treatment discontinuation, only adverse reactions were collected.* The adverse reactions that led to treatment discontinuation occurred in 10 of 61 subjects (16.4%) in the trabectedin group, and 6 of 57 subjects (10.5%) in the DOX group. These adverse reactions were ALT increased (4 subjects, 6.6%), AST increased, and thrombocytopenia (3 subjects each, 4.9%), GGT increased (2 subjects each, 3.3%), and rhabdomyolysis, neutropenia, blood bilirubin increased, blood ALP increased, blood CPK increased, and liver injury (1 subject each, 1.6%) in the trabectedin group; and ejection fraction decreased (2 subjects, 3.5%), and pneumonia, thrombocytopenia, inflammation mucous membrane, and febrile neutropenia (1 subject each, 1.8%) in the DOX group.

* In this study, there were no data on adverse events which led to treatment discontinuation other than those on the adverse reactions.

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 assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

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

The assessment is ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

PMDA has concluded that the submitted data demonstrate a certain degree of efficacy of trabectedin in treating soft tissue sarcomas and its safety is acceptable in view of its observed benefits. Trabectedin, a drug with a new active ingredient, binds to the DNA minor groove, thereby inhibiting the nucleotide excision repair pathway and performing other actions, resulting in the suppression of tumor growth. Trabectedin is a clinically meaningful treatment option for soft tissue sarcomas. Its indications, dosage and administration, post-marketing investigation, and other issues will be further discussed in the Expert Discussion.

Trabectedin may be approved if the drug is considered to have no particular problems based on comments from the Expert Discussion.

Review Report (2)

August 18, 2015

I. Product Submitted for Registration

[Brand name]	Yondelis I.V. infusion 0.25 mg, Yondelis I.V. infusion 1 mg
[Non-proprietary name]	Trabectedin
[Applicant]	Taiho Pharmaceutical Co., Ltd.
[Date of application]	January 5, 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

Based on the discussion in "II.4.(iii).B.(2) Efficacy" of Review Report (1), PMDA concluded that trabectedin has a certain degree of efficacy for patients previously treated with chemotherapy for unresectable soft tissue sarcoma (STS) of histological subtypes reported to carry chromosomal translocations, for reasons including the following: In the Japanese phase II study (Study 10045030) conducted in this patient population, trabectedin was shown to be superior to best supportive care in the primary endpoint, namely progression-free survival assessed by the independent radiology review committee.

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

(2) Safety

Based on the discussion in "II.4.(iii).B.(3) Safety" of Review Report (1), PMDA concluded that close attention is required in the treatment with trabectedin especially for the following adverse events: bone marrow depression, febrile neutropenia, hepatic dysfunction, gastrointestinal disorder, rhabdomyolysis, injection site reaction, hypersensitivity, secondary malignancy, and pancreatitis.

PMDA concluded that the tolerability of trabectedin is acceptable provided that trabectedin is administered by a physician with sufficient knowledge and experience in cancer chemotherapy, with close monitoring and control of adverse events, and that appropriate action in response to adverse events is taken including treatment interruption, dose reduction, or treatment discontinuation.

This conclusion by PMDA was supported by the expert advisors at the Expert Discussion. Furthermore, the following issues were raised by the expert advisors:

- Since the incidence of rhabdomyolysis associated with antineoplastic agents is generally low, physicians with thorough knowledge and experience in chemotherapy may have only limited experience in treating patients with rhabdomyolysis. Therefore, healthcare professionals should be advised to closely monitor creatine phosphokinase (CPK) on a regular basis [see "II.4.(iii).B.(3).5) Rhabdomyolysis" of Review Report (1)], and should be informed appropriately of the clinical course of patients who experienced rhabdomyolysis in clinical studies, because such information would lead to early detection of rhabdomyolysis.

Based on the issues raised in the Expert Discussion, PMDA has concluded that the applicant should appropriately inform healthcare professionals of the clinical course of patients who experienced rhabdomyolysis in the Japanese clinical studies, using information materials etc.

PMDA instructed the applicant to take appropriate measures according to the above advice. The applicant agreed.

(3) Clinical positioning and indications

As discussed in the "II.4.(iii).B.(4) Clinical positioning and indications" of Review Report (1), the clinical benefit of trabectedin has been demonstrated in patients enrolled in Study 10045030. PMDA therefore concluded that the indication for trabectedin should be "soft tissue sarcomas," and that the "Precautions for indication" section should include the following precautionary information.

- The efficacy and safety of trabectedin have not been established in patients with histopathological subtypes not evaluated in the clinical studies.
- The efficacy and safety of trabectedin have not been established in chemotherapy-naïve patients.
- Prior to determining whether a patient is eligible for trabectedin therapy, carefully read the "Clinical studies" section of the package insert, fully understand the efficacy and safety of trabectedin, and carefully consider other treatment options.

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

PMDA instructed the applicant to define the "Indication" and "Precautions for indication" as above. The applicant agreed.

(4) Dosage and administration

PMDA's conclusion based on the discussion in the "4.(iii).B.(5) Dosage and administration" in Review Report (1):

The dosage and administration of trabectedin should be as follows: "The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition," as proposed by the applicant. The "Precautions for dosage and administration" section should provide the following precautionary information:

- The efficacy and safety of trabectedin co-administered with other antineoplastic agents have not been established.
- Trabectedin should be administered via the central vein.
- Criteria for treatment interruption, dose reduction, and treatment discontinuation in case of adverse reactions.

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

PMDA instructed the applicant to define the "Dosage and administration" and "Precautions for dosage and administration," as shown below. The applicant agreed.

Dosage and administration

The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. The dose should be reduced according to the patient's condition.

Precautions for dosage and administration

1. The efficacy and safety of trabectedin co-administered with other antineoplastic agents have not been established.
2. Trabectedin should be administered via the central vein because extravasation of the agent may cause severe tissue damage.
3. Reconstitute the product with physiological saline (5 mL for Yondelis I.V. infusion 0.25 mg, 20 mL for Yondelis I.V. infusion 1 mg) to make trabectedin 0.05 mg/mL solution. Using a syringe, draw up the required volume of the reconstituted solution for further dilution with ≥ 500 mL of physiological saline.
4. If necessary, treatment should be interrupted or dose should be reduced according to the criteria below.
   (1) If the laboratory values at baseline do not meet the "Criteria for starting treatment with trabectedin," trabectedin should not be administered, or treatment should be delayed until the criteria are met.

Criteria for starting treatment with trabectedin

Parameter	Criteria
Neutrophil count	≥1500/mm^3
Haemoglobin	≥9.0 g/dL

Platelet count	≥10 × 10^4/mm^3
Albumin	≥2.5 g/dL
Bilirubin total	≤1.5 mg/dL
Aspartate aminotransferase	≤2.5 × upper limit of normal (ULN)
Alanine aminotransferase	
Alkaline phosphatase*1	
CPK	
Creatinine clearance*2	≥30 mL/min

*1, This criterion does not apply if abnormal alkaline phosphatase is attributable to the primary disease.
*2, Values should be calculated according to the Cockcroft-Gault equation. If creatinine clearance is actually measured, the measured value must meet this criterion.

(2) In case of an adverse reaction meeting the "Criteria for dose reduction," the dose must be reduced by 1 level at a time, but not to less than 0.8 mg/m^2, the minimum dose.

Criteria for dose reduction

Parameter	Criteria
Neutrophil count	<500/mm^3 persisting for ≥6 days; or <500/mm^3 with fever or infection
Platelet count	<2.5 × 10^4/mm^3
Bilirubin total	>1.5 mg/dL
Aspartate aminotransferase	>2.5 × ULN on Day 21 or later
Alanine aminotransferase	
Alkaline phosphatase	>2.5 × ULN
Non-hematological toxicity	≥ Grade 3*

* In accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Dose reduction levels

Reduction	Dose
Recommended dose	1.2 mg/m^2
First dose reduction	1.0 mg/m^2
Second dose reduction	0.8 mg/m^2

(5) Risk Management Plan (draft)

The applicant has planned a post-marketing surveillance covering all patients with STS who will receive trabectedin, to primarily investigate the safety of trabectedin in clinical use after the market launch. The target sample size is 150 subjects with an observation period of 48 weeks (a maximum of 16 cycles). The proposed priority investigation items are hepatic dysfunction, bone marrow depression, serious hypersensitivity, rhabdomyolysis/CPK increased, injection site reaction, and presence/absence of hepatic impairment prior to trabectedin treatment.

Based on the discussion in the "4.(iii).B. (6) Post-marketing investigations" in Review Report (1), PMDA concluded that it is necessary to conduct an all-case surveillance covering all patients who receive trabectedin to primarily investigate the safety of trabectedin in clinical use. PMDA's view on the surveillance plan is presented below:

- The surveillance should be designed to investigate risk factors for hepatic dysfunction and bone marrow depression.

- The priority investigation items must include hepatic failure/hepatic dysfunction, bone marrow depression/febrile neutropenia, and rhabdomyolysis, but need not include serious hypersensitivity or injection site reaction.
- The target sample size and the observation period should be re-examined to allow the assessment of the risk factors, taking account of clinical study data regarding the occurrence of adverse events included in the priority investigation items.

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

Based on the above, PMDA instructed the applicant to reconsider the surveillance plan.

The applicant's response:

- The surveillance will be designed to primarily investigate risk factors for the occurrence of hepatic dysfunction and bone marrow depression. The risk factors are sex, age, complications, presence/absence of metastasis to liver, the performance status at baseline, number of previous regimens, baseline hepatic function, initial dose level of trabectedin, and baseline neutrophil count.* Analyses of the risk factors for the occurrence of hepatic dysfunction and bone marrow depression will be performed using multiple logistic regression models.
- The target sample size is 140 subjects. This will allow evaluation of the risk factors for the occurrence of hepatic dysfunction and bone marrow depression.
- The observation period should be 24 weeks, taking account of the time of onset of hepatic dysfunction and bone marrow depression in studies including Study 10045030.
- The priority investigation items should be changed as instructed by PMDA. The presence/absence of hepatic impairment prior to trabectedin treatment should be surveyed as patient characteristics, and CPK increased should be recorded as an abnormal laboratory value related to rhabdomyolysis.

* This should be assessed as a risk factor for bone marrow depression.

PMDA accepted the applicant's explanation.

Based on the above discussion, PMDA concluded that the risk management plan (draft) should include the following safety and efficacy specifications, and the applicant should perform additional pharmacovigilance actions and risk minimization actions (see the tables below).

Safety and efficacy specifications for the Risk Management Plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hepatic failure/hepatic dysfunction • Bone marrow depression/ febrile neutropenia/infections • Rhabdomyolysis • Tissue disorder caused by extravasation	• Secondary malignancy • Pancreatitis • Serious hypersensitivity	• Treatment in patients with hepatic dysfunction
Efficacy specifications		
• Efficacy for STS in clinical use		

Summary of additional pharmacovigilance and risk minimization actions for the Risk Management Plan (draft)

Additional pharmacovigilance actions	Additional risk minimization actions
• Early post-marketing phase vigilance • Post-marketing surveillance (all-case surveillances; see the table below for the outline of the draft plan) • Post-marketing clinical study (switched from Study 10045050)	• Information provision by implementing an early post-marketing phase vigilance program • Preparation and distribution of materials for healthcare professionals (guideline for proper use of trabectedin)

Outline of post-marketing surveillance plan (draft)

Objective	(1) To evaluate risk factors for the occurrence of hepatic dysfunction and bone marrow depression (2) To assess the safety and other data of trabectedin in clinical use
Method	All-case surveillance
Population	Patients with STS
Observation period	24 weeks
Target sample size	140 subjects
Main investigation items	Priority investigation items, hepatic failure/hepatic dysfunction, bone marrow depression/febrile neutropenia, and rhabdomyolysis. Main investigation items other than above, patient characteristics (e.g., sex, age, complications, presence/absence of metastasis to liver, baseline performance status, number of previous regimens, baseline hepatic function, and baseline neutrophil count), status of treatment with trabectedin, co-administered agents or combination therapy, and adverse events, etc.

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

A document-based compliance inspection of the data submitted in the new drug application was conducted 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. PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the New Drug Application (5.3.3.2.1, 5.3.5.1.1, and 5.3.5.2.1). The results showed satisfactory overall GCP compliance in the conduct of clinical studies, and PMDA therefore concluded that there should be no problem in conducting a regulatory review based on the submitted application documents. However, the following issue was found regarding the study sponsor, albeit with no major impact on the overall study evaluation, and was notified to the applicant (sponsor) as an issue to be improved.

Issue to be improved

Sponsor

- Delay in periodic safety reporting to the study site director.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that trabectedin may be approved for the following indication and dosage and administration, with the conditions for approval shown below, provided that cautionary advice and information on proper use are provided appropriately in the package insert and other information materials after market release, and that trabectedin is properly used by a physician with sufficient knowledge and experience of cancer chemotherapy, in a medical facility well equipped to deal with emergencies. Since trabectedin is an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as poisonous drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]

Soft tissue sarcomas

[Dosage and administration]

The usual adult dosage is 1.2 mg/m^2 (body surface area) of trabectedin, administered as an intravenous infusion over 24 hours, with an interval of at least 20 days between cycles. This treatment cycle should be repeated. The dose should be reduced according to the patient's condition.

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of the very limited number of subjects included in Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until the data for the planned number of patients are accumulated, thereby identifying the characteristics of treated patients, collecting data on the safety and efficacy of the product as soon as possible, and taking necessary measures to ensure its proper use.

[Warnings]

Trabectedin should be administered only to patients considered eligible by a physician with sufficient knowledge and experience of cancer chemotherapy, in a medical institution capable of properly dealing with emergencies. Before starting treatment, fully inform the patient or his/her family members about the benefits and risks of trabectedin and obtain the consent from them.

[Contraindications]

1. Patients with a history of serious hypersensitivity to any ingredient of the product
2. Women who are or may be pregnant

[Precautions for indication]

1. The efficacy and safety of trabectedin have not been established in chemotherapy-naïve patients.

2. The efficacy and safety of trabectedin have not been established in patients with histopathological subtypes not evaluated in the clinical studies.
3. Prior to determining whether a patient is eligible for trabectedin therapy, carefully read the “Clinical studies” section of the package insert, fully understand the efficacy and safety of trabectedin, and carefully consider other treatment options.

[Precautions for dosage and administration]

1. The efficacy and safety of trabectedin co-administered with other antineoplastic agents have not been established.
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4. If necessary, treatment should be interrupted or dose should be reduced according to the criteria below.
   (1) If the laboratory values prior to starting treatment with trabectedin do not meet the “Criteria for starting treatment with trabectedin,” trabectedin should not be administered, or treatment should be delayed until the criteria are met.

Criteria for starting treatment with trabectedin

Parameter	Criteria
Neutrophil count	≥1500/mm^3
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Platelet count	≥10 × 10^4/mm^3
Albumin	≥2.5 g/dL
Bilirubin total	≤1.5 mg/dL
AST (GOT)	≤2.5 × upper limit of normal (ULN)
ALT (GPT)	
ALP[*1]	
CK (CPK)	
Creatinine clearance[*2]	≥30 mL/min

*1, This criterion does not apply if abnormal ALP is attributable to the primary disease.
*2, Values should be calculated according to the Cockcroft-Gault equation. If creatinine clearance is actually measured, the measured value must meet this criterion.

(2) In case of an adverse reaction meeting the "Criteria for dose reduction," the dose must be reduced by 1 level at a time, but not to less than 0.8 mg/m^2, the minimum dose.

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Parameter	Criteria
Neutrophil count	<500/mm^3 persisting for ≥6 days; or <500/mm^3 with fever or infection
Platelet count	<2.5 × 10^4/mm^3
Bilirubin total	>1.5 mg/dL
AST (GOT)	>2.5 × ULN on Day 21 or later
ALT (GPT)	
ALP	>2.5 × ULN
Non-hematological toxicity	≥ Grade 3[*]

* In accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Dose reduction levels

Reduction	Dose
Recommended dose	1.2 mg/m^2
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