Report on the Deliberation Results

May 17, 2022

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Darvias Injection 135 mg
Non-proprietary Name	Darinaparsin (JAN*)
Applicant	Solasia Pharma K.K.
Date of Application	June 30, 2021

Results of Deliberation

In its meeting held on May 12, 2022, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients are collected to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

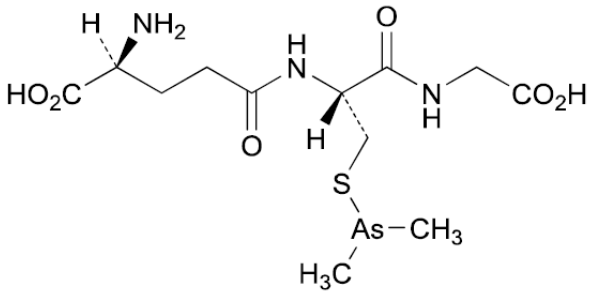
Review Report

April 14, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Darvias Injection 135 mg
Non-proprietary Name	Darinaparsin
Applicant	Solasia Pharma K.K.
Date of Application	June 30, 2021
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection, each vial containing 150 mg of darinaparsin
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{12}H_{22}AsN_3O_6S$
Molecular weight: 411.31
Chemical name: L-γ-Glutamyl-*S*-(dimethylarsanyl)-L-cysteinylglycine

Items Warranting Special Mention	None
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of relapsed or refractory peripheral T-cell lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, peripheral nervous system disorders, and QT interval prolongation should be further investigated through post-marketing surveillance.

Indication

Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration

The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over 1 hour for 5 days, followed by a 16-day rest period. This 21-day treatment cycle should be repeated. The dose may be reduced, as appropriate, according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients are collected to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

February 25, 2022

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Darinasia Injection 135 mg
Non-proprietary Name	Darinaparsin
Applicant	Solasia Pharma K.K.
Date of Application	June 30, 2021
Dosage Form/Strength	Lyophilized powder to be reconstituted before injection, each vial containing 150 mg of darinaparsin
Proposed Indication	Relapsed or refractory peripheral T-cell lymphoma

Proposed Dosage and Administration

The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over approximately 1 hour for 5 consecutive days, followed by a 16-day rest period. This cycle should be repeated. The dose may be reduced according to the patient's condition as necessary.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Darinaparsin is an organic arsenic compound with a glutathione conjugate discovered by the University of Texas M. D. Anderson Cancer Center (US) and Texas A&M University (US). Darinaparsin is one of the metabolic intermediates formed in the *in vivo* metabolic process of inorganic arsenic compounds (*Annu Rev Pharmacol Toxicol*. 2007;47:243-62). Upon internalization into the cells via cystine transporters expressed on the cell membrane surface of tumor cells (*Mol Pharmacol*. 2014;85:576-85), darinaparsin causes various effects including a decrease in mitochondrial membrane potential, thereby enhancing production of intracellular reactive oxygen species (ROS). This and other factors are thought to induce apoptosis and cell cycle arrest, thereby exerting antitumor effects.

1.2 Development history etc.

Outside Japan, a US-based company, ZIOPHARM Oncology, Inc. (currently, Alaunos Therapeutics, Inc., US) initiated a phase I study (Study SGL1001) in patients with relapsed or refractory hematopoietic malignancies in May 2005. The applicant initiated a global phase II study (Study 02) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) in March 2016.

As of January 2022, darinaparsin has not been approved in any country or region.

In Japan, the applicant initiated a phase I study (Study 01) in patients with relapsed or refractory PTCL in February 2012, and patient registration for Study 02 mentioned above began in March 2016.

Recently, the applicant has filed a marketing application for darinaparsin with the pivotal data from Study 02.

A brand name of "Darinasia Injection 135 mg" had been proposed for darinaparsin in the application; however, it was changed to "Darvias Injection 135 mg" at the applicant's request.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to grayish white crystalline powder. Its description, pH, partition coefficient, solubility, and hygroscopicity were determined, as well as powder X-ray diffraction, thermogravimetry, and differential scanning calorimetry characteristics.

The chemical structure of the drug substance has been elucidated by proton- and ^{13}C-nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), ultraviolet spectroscopy (UV), infrared absorption spectroscopy (IR), elemental analysis, and mass spectrometry (MS).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted], the intermediate. [redacted] has been registered in a master file (MF) (MF registration number: [redacted]) by [redacted] Co., Ltd. See Attachment for the manufacturing process.

The quality control strategy (Table 1) has been formulated for the manufacturing process of intermediate [redacted] and subsequent steps based on the following.

- Identification of critical quality attributes (CQAs).
- Identification of critical process parameters (CPPs) according to quality risk assessment and experimental design, and determination of the proven acceptable range (PAR) for manufacturing process parameters.

Table 1. Summary of control strategies for drug substance

CQA	Control method
Content	Specifications
Description (appearance)	[redacted], specifications
Identification	Specifications
Elemental impurities	[redacted], specifications
Related substances	[redacted], specifications
Residual solvents	[redacted], specifications
Water content	[redacted], specifications
Bacterial endotoxins	Specifications
Microbial limit	Specifications
[redacted]	Specifications

The step for [redacted] reaction of [redacted] and [redacted] has been defined as a critical process step, and process control items and values have been specified. [redacted] is controlled as a critical intermediate.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (^{1}H-NMR and high performance liquid chromatography [HPLC]), purity (elemental impurities [inductively coupled plasma-mass spectrometry], related substances [HPLC], and residual solvents [gas chromatography (GC) and HPLC]), water content, bacterial endotoxins, microbial limit, [redacted] (inductively coupled plasma-mass spectrometry), and assay (HPLC).

2.1.4 Stability of drug substance

The main stability study for the drug substance (Table 2) demonstrated that the drug substance is stable. A photostability study was conducted and the results demonstrated that the drug substance is photolabile.

Table 2. Stability study of drug substance

Study	Primary batch	Temperature	Storage package	Storage period
Long-term	3 commercial batches	[redacted] ± [redacted]°C	Double-layer FEP bag + fiber drum	36 months

On the basis of the above results, a retest period of 36 months was proposed for the drug substance when placed in double-layer fluorinated ethylene propylene copolymer (FEP) bags and stored protected from light in a fiber drum at ≤[redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection supplied in a vial containing 150 mg of the drug substance. Excipients contained in the drug product are hydrochloric acid and sodium hydroxide. Each vial contains an overfill above the labeled amount to allow the withdrawal of 135 mg of the drug substance after reconstitution with 1.8 mL of water for injection.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising drug solution preparation, aseptic filtration, filling, lyophilization, capping, and packaging and labeling.

The quality control strategy (Table 3) has been formulated based on the following.

- Identification of CQAs.
- Identification of CPPs according to quality risk assessment and determination of the PAR for manufacturing process parameters.

Table 3. Summary of control strategies for drug product

CQA	Control method
Strength	[redacted], specifications
Description	[redacted], specifications
Identification	[redacted], specifications
pH	[redacted], specifications
Appearance of solution (turbidity, color)	[redacted], specifications
Related substances	[redacted], specifications
Water content	[redacted], specifications
Bacterial endotoxins	[redacted], specifications
Uniformity of dosage units	[redacted], specifications
Foreign insoluble matter	[redacted], specifications
Insoluble particulate matter	[redacted], specifications
Sterility	[redacted], specifications
Reconstitution time	[redacted], specifications

The steps for [redacted], [redacted], and [redacted] have been defined as critical process steps. Process control has been specified for [redacted], [redacted], [redacted], and [redacted] steps.

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC and high performance liquid chromatography-mass spectrometry [HPLC-MS]), pH, purity (appearance of solution, related substances [HPLC]), water content, bacterial endotoxins, uniformity of dosage units (mass variation test), foreign insoluble matter, insoluble particulate matter, sterility, reconstruction time, and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows main stability studies conducted for the drug product. The results of the long-term testing demonstrated that the drug product is stable for up to 36 months except for the result at Month [redacted]. [redacted][1)] was observed in 1 batch at Month [redacted]. The applicant explained that the [redacted] is [redacted]-related and is not considered to be a quality change associated with storage. The results of the accelerated testing demonstrated that the drug product is stable. A photostability study was conducted, and the results demonstrated that the drug product is photolabile.

Table 4. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial batches	5 ± 3°C	—	Butyl rubber stopper + glass vial	36 months
Accelerated	3 commercial batches	25 ± 2°C	60 ± 5%RH		6 months

—, not controlled

On the basis of the above, a shelf life of 36 months has been proposed for the drug product when stored at 2°C to 8°C in a glass vial with a butyl rubber stopper in a carton protected from light.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled. Data relating to MF have been submitted for darinaparsin separately by the MF holder. See Attachment for the results of review on MF conducted by PMDA.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Effects on mitochondria (CTD 4.2.1.1.2, 4.2.1.1.5)

Using human acute promyelocytic leukemia (APL) HL-60 cell lines, the effect of darinaparsin on mitochondrial membrane potential was investigated by flow cytometry. The uptake of basic fluorescent dye into living cell-derived mitochondria was used as an index, and the results indicated that darinaparsin decreased mitochondrial membrane potential.

Mitochondria were isolated from MOLT-4 cell lines derived from human acute T-lymphoblastic leukemia (T-ALL) and then treated with darinaparsin. Using the supernatant from the darinaparsin-treated solution, the effect of darinaparsin on the release of cytochrome c from mitochondria was investigated by the Western blot method with cytochrome c expression as an index. The results indicated that darinaparsin increased the release of cytochrome c.

Using mitochondria isolated from MOLT-4 cell lines, the effect of darinaparsin on mitochondrial swelling was investigated by measuring absorbance at a wavelength of 540 nm. The results indicated

1) Because the detected [redacted] was [redacted] from [redacted] at [redacted], an improvement measure was implemented to change to [redacted] so as to meet more stringent control criteria for [redacted]. Analysis results of batches manufactured using [redacted] after change have shown no [redacted].

that darinaparsin decreased the absorbance (i.e., mitochondrial swelling) at that wavelength. On the other hand, mitochondrial swelling caused by darinaparsin was not observed in the presence of ciclosporin A, a mitochondrial permeability transition pore (mPTP) inhibitor.

3.1.2 Enhancement of production of intracellular reactive oxygen species (CTD 4.2.1.1.2)

Using HL-60 cell lines, the effect of darinaparsin on the production of intracellular reactive oxygen species (ROS), e.g., superoxide and hydrogen peroxide (H_2O_2), was investigated by flow cytometry with dihydroethidium oxidation or 5,6-carboxy-2',7'-dichlorofluorescein-diacetate (CM-H_2DCFDA) oxidation as an indicator. The results indicated that darinaparsin enhanced production of intracellular ROS.

3.1.3 Induction of apoptosis (CTD 4.2.1.1.2)

Using HL-60 cell lines, the ability of darinaparsin to induce apoptosis was investigated by (1) flow cytometry[2)] with annexin V staining or caspase-3 activity as an indicator; and (2) the Western blotting technique with an indicator such as caspase-9 activity. Both methods indicated that darinaparsin induced apoptosis.

3.1.4 Induction of cell cycle arrest (CTD 4.2.1.1.2)

Using human APL NB4 and HL-60 cell lines, the ability of darinaparsin to induce cell cycle arrest was investigated by flow cytometry with propidium iodide (PI) staining as an indicator. The results showed that in both cell lines darinaparsin induced G2/M cell cycle arrest. In HL-60 cell lines, however, darinaparsin did not induce G2/M cell cycle arrest in the presence of *N*-acetyl cysteine, a precursor of glutathione, which is a ROS production inhibitor.

3.1.5 Antiproliferative effect on hematopoietic malignant cell lines

3.1.5.1 *In vitro* (CTD 4.2.1.1.1, 4.2.1.1.2)

The antiproliferative effect of darinaparsin on the human T-ALL Jurkat cell line, and the human cutaneous T-cell lymphoma (CTCL) cell lines (HH and Hut78) was investigated with living cell-derived reductase activity as an index. The IC_{50} of darinaparsin was 2.7, 3.2, and 6.7 μmol/L, respectively.

The antiproliferative effect of darinaparsin on human hematopoietic malignant cell lines was investigated using living cell-derived reductase activity as an index. Table 5 shows the results.

2) Necrotic cells were stained with PI and eliminated.

Table 5. Antiproliferative effect of darinaparsin on human hematopoietic malignant cell lines

Cell line	Derived from	IC_{50} (μmol/L)
NB4	APL	2.3
HL-60		2.9
KBM5	CML	4.7
KBM7		1.9
Z-119	T-ALL	4.4

n = 3

3.1.5.2 *In vivo* (CTD 4.2.1.1.7)

Multiple myeloma (MM) patient-derived LAGλ-1 tumor fragments were intramuscularly transplanted into severe combined immunodeficiency (SCID) mice (n = 5/group) to investigate the antitumor effect of darinaparsin. From Day 14 to 35 (transplantation on Day 0), each xenograft-bearing mouse received one of the following treatments and tumor volume was calculated: (1) darinaparsin 50 or 100 mg/kg IV BID 5 days a week; (2) darinaparsin 100 or 200 mg/kg IV QD once a week; or (3) darinaparsin 100 or 200 mg/kg IV QD 3 days a week. Darinaparsin tended to exert antitumor effects in the 200 mg/kg group in treatment regimens (2) and (3) compared with the control (saline) group.

3.2 Safety pharmacology

3.2.1 Effects on the central nervous system (CTD 4.2.1.3.1)

A single intravenous dose of darinaparsin 50, 75, or 150 mg/kg was administered to rats (n = 6/group) and the effects of darinaparsin on clinical signs and neurobehavioral function were evaluated by the modified Irwin procedure. The results showed a decrease in locomotor activity in the darinaparsin 75 and 150 mg/kg groups and salivation in the darinaparsin 150 mg/kg group.

The C_{max} of arsenic in plasma (2,669 ng/mL) in rats at darinaparsin 45 mg/kg exceeded the C_{max} of arsenic in plasma (1,359 ng/mL[3)]) at the recommended clinical dose. On the basis of this and other findings, safety-related problems are unlikely to emerge in clinical settings; however, given that darinaparsin was shown to have an effect on the central nervous system in the repeated toxicity study in dogs [see Section 5.R.1] and nervous system disorders were reported in the clinical studies [see Section 7.R.3.5], the applicant explained that a cautionary statement regarding central nervous system disorders will be provided to healthcare professionals in an appropriate manner using the package insert or other materials.

3.2.2 Effects on the cardiovascular system

3.2.2.1 Effects on hERG potassium current (CTD 4.2.1.3.2)

The effects of darinaparsin on human *ether-a-go-go* related gene (hERG) potassium current was evaluated using the human embryonic kidney 293 (HEK293) cell line transfected with hERG. The percentage inhibition of hERG potassium current at darinaparsin 30, 100, 300, and 1,000 μmol/L was −0.1 ± 0.3%, 11.1 ± 1.6%, 13.2 ± 1.7%, and 11.9 ± 0.7%, respectively (mean ± standard error; n = 3).

3) The C_{max} on Day 5 (steady state) following intravenous administration of darinaparsin 300 mg/m^2 on Days 1 to 5 in the global phase II study (Study 02) [see Section 6.2.2.1].

Compared with the control, i.e., 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES) buffered saline,[4)] inhibition was statistically significant at darinaparsin 100, 300, and 1,000 μmol/L (P <0.05 for all the groups; Dunnett's test for multiple comparison).

3.2.2.2 Effects on electrocardiogram, heart rate, and blood pressure (CTD 4.2.1.3.4, 4.2.1.3.5, 4.2.1.3.6, and 4.2.1.3.7)

Isolated guinea pig hearts were perfused by the Langendorff technique, and the effects of darinaparsin 0.01, 0.1, 1, 10, and 100 μmol/L on the electrocardiogram (RR interval, PQ interval, QRS interval, QT interval, QTc interval, and ST-T interval) and maximum/minimum rates of rise of left ventricular pressure (dP/dt_{max} and dP/dt_{min}) were investigated. Prolongation of RR, PQ, QRS, QT, QTc, and ST-T intervals, decrease in dP/dt_{max}, and increase in dP/dt_{min} were observed at darinaparsin 100 μmol/L.

Single intravenous doses of darinaparsin 2, 4, and 6 mg/kg were administered to dogs (N = 8) in the sequential order of doses to evaluate the effects of darinaparsin on the electrocardiogram (QRS, PR, QT, and QTc intervals), heart rate, and blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure). The results indicated no effects of darinaparsin.

Single intravenous doses of darinaparsin 8, 15, and 30 mg/kg were administered to dogs (N = 8) in the sequential order of doses to evaluate the effects of darinaparsin on the electrocardiogram (RR, QRS, PR, QT, and QTc intervals, T-peak to T-end interval [$T_{P\text{-}E}$ interval], QRS potential and ST potential), heart rate, and blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure). The results showed shortening of RR and PR intervals, increase in heart rate, and rises in systolic blood pressure, diastolic blood pressure, and mean arterial pressure at darinaparsin 30 mg/kg.

Single intravenous doses of darinaparsin 8, 15, and 30 mg/kg were administered to dogs (N = 4) in the sequential order of doses to evaluate the effects of darinaparsin on the electrocardiogram (QRS, PR, QT, and QTc intervals), heart rate, and blood pressure (systolic blood pressure, diastolic blood pressure, and mean arterial pressure). The results showed increase in heart rate and rises in systolic blood pressure, diastolic blood pressure, and mean arterial pressure at darinaparsin 30 mg/kg.

The applicant's explanation about the findings above:

- QTc interval prolongation was reported also in the 18-week repeated-dose toxicity study in dogs [see Section 5.2] and QT interval prolongation and other findings were reported in the clinical studies [see Section 7.R.3.6]; therefore, a cautionary statement regarding electrocardiogram anomalies will be provided to healthcare professionals in an appropriate manner using the package insert or other materials.
- The C_{max} of arsenic in plasma (4,194 ng/mL) in dogs at darinaparsin 30 mg/kg exceeded the C_{max} of arsenic in plasma (1,359 ng/mL[3)]) at the recommended clinical dose. On the basis of this and

[4)] 137 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1.0 mmol/L magnesium chloride, 10 mmol/L HEPES and 10 mmol/L glucose.

other findings, safety-related problems associated with blood pressure rise and increased heart rate are unlikely to emerge in clinical settings.

3.2.3 Effects on the respiratory system (CTD 4.2.1.3.6)

Single intravenous doses of darinaparsin 8, 15, and 30 mg/kg were administered to dogs (N = 8) in the sequential order of doses to evaluate the effects of darinaparsin on respiratory rate and tidal volume. An increase in respiratory rate was noted at darinaparsin 30 mg/kg.

The C_{max} of arsenic in plasma (4,194 ng/mL) in dogs at darinaparsin 30 mg/kg exceeded the C_{max} of arsenic in plasma (1,359 ng/mL[3)]) at the recommended clinical dose. On the basis of this and other findings, the applicant explained that safety-related problems are unlikely to emerge in clinical settings.

3.3 Pharmacodynamic drug interactions (CTD 4.2.1.4.2)

Using 3 types of human T-ALL cell lines, antiproliferative effects of darinaparsin, forodesine, pralatrexate, and romidepsin alone, and darinaparsin in combination with forodesine, pralatrexate, or romidepsin were investigated with living cell-derived reductase activity as an index. Table 6 shows the IC_{50} and combination index values[5)] of darinaparsin, forodesine, pralatrexate, and romidepsin against each cell line.

Table 6. Antiproliferative effects of darinaparsin, forodesine, pralatrexate, and romidepsin against human T-ALL cell lines

Combination drug	Cell line	IC_{50} (μmol/L)			Combination index*2
		Darinaparsin alone	Combination drug alone	Darinaparsin/combination drug*1	
Forodesine	Jurkat	2 ± 0.1	0.01 ± 0.00	1.00 ± 0.08	0.9
	CCRF-CEM	3 ± 0.6	0.003 ± 0.000	0.22 ± 0.05	1
	MOLT-4	1.1 ± 0.2	0.003 ± 0.002	0.51 ± 0.29	0.46
Pralatrexate	Jurkat	1.4 ± 0.0	0.002 ± 0.000	0.02 ± 0.00	0.76
	CCRF-CEM	1.9 ± 0.3	0.002 ± 0.001	0.22 ± 0.03	0.55
	MOLT-4	2 ± 0.2	0.002 ± 0.001	0.20 ± 0.02	0.48
Romidepsin	Jurkat	2.6 ± 0.3	0.005 ± 0.001	0.55 ± 0.25	1.22
	CCRF-CEM	1.2 ± 0.1	0.001 ± 0.000	0.14 ± 0.00	3.7
	MOLT-4	0.94 ± 0.06	0.003 ± 0.000	0.25 ± 0.08	2.2

Mean ± standard deviation; n = 3; *1, IC_{50} of darinaparsin when darinaparsin and the concomitant drug were used at a molar concentration ratio of 100:1; *2, combination index <0.8 was defined as "synergistic effect," combination index 0.8-1.2 as "additive effect," and combination index >1.2 as "antagonistic effect."

3.R Outline of the review conducted by PMDA

PMDA concluded that the applicant's explanation about the non-clinical pharmacology of darinaparsin is acceptable based on the submitted data and discussions in the following sections.

5) Calculated based on the method by Chou and Talalay (*Cancer Res.* 2010;70:440-6).

3.R.1 Mechanism of action and efficacy of darinaparsin

The applicant's explanation about the mechanism of action of darinaparsin and its efficacy against PTCL:

Cystine transporters, a class of amino acid transporters, are involved in cellular uptake of extracellular cystine in exchange for glutamate. It is reported that xCT, a component of cystine transporter, is overexpressed in tumor cells, contributing to stabilization of cystine transporters (e.g., *Am J Cancer Res*. 2020;10:3106-26).

Darinaparsin is one of the metabolic intermediates formed in the *in vivo* metabolic process of inorganic arsenic compounds (*Annu Rev Pharmacol Toxicol*. 2007;47:243-62). Darinaparsin is metabolized into S-(dimethylarsino)-L-cystein, a trivalent arsenic compound, by γ-glutamyl transpeptidase (γ-GT) that is expressed on cell membrane surface, and taken up into the cells via cystine transporters (*Mol Pharmacol*. 2014;85:576-85).

Pyruvic acid formed in glycolysis is used for adenosine triphosphate (ATP) production via the mitochondrial electron transport chain. It has been suggested that trivalent arsenic compounds cause mitochondrial dysfunction by inhibiting the activity of the pyruvate dehydrogenase complex, which converts pyruvic acid into acetyl-CoA (*Toxicol Lett*. 2002;133:1-16).

On the basis of the above, darinaparsin, after being transported into cells as S-(dimethylarsino)-L-cystein, causes mitochondrial dysfunction (e.g., decrease in membrane potential) via mechanisms including those discussed above [see Section 3.1.1], thereby enhancing production of intracellular ROS [see Section 3.1.2]. This and other factors are thought to induce apoptosis and cell cycle arrest [see Sections 3.1.3 and 3.1.4], thereby exerting antitumor effects.

Darinaparsin showed antiproliferative effects on hematopoietic malignancy-derived cell lines including human T cell tumor-derived cell lines [see Section 3.1.5.1]. Although no data are available from non-clinical studies evaluating the antiproliferative effects of darinaparsin against the human PTCL cell line, given this and other factors, together with the mechanism of action, darinaparsin is expected to show efficacy also against PTCL, a type of T cell tumors.

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Animal studies of arsenic[6)] pharmacokinetics (PK) were conducted in rats and dogs. Human or animal biological samples were used for plasma protein binding of darinaparsin, drug-metabolizing enzymes, transporters, and other evaluations.

6) Darinaparsin is one of the metabolic intermediates formed in the *in vivo* metabolic process of inorganic arsenic compounds. Because of the above and other reasons, PK after administration of darinaparsin was evaluated using arsenic as an indicator.

4.1 Absorption

4.1.1 Single-dose study

A single intravenous dose of darinaparsin 30 mg/kg was administered to male dogs to investigate plasma and blood arsenic concentrations (Table 7). The blood-to-plasma arsenic concentration ratio immediately before the end of infusion was 3.4.

Table 7. PK parameters of arsenic (male dogs, single intravenous dose)

Sample	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	$V_{d,ss}$ (mL/kg)
Plasma	3.79 ± 0.321	23.3 ± 3.04	5.05 ± 0.881	237 ± 33.0	1,210 ± 92.4
Blood	10.2 ± 3.29	26.9 ± 3.45	6.62 ± 1.15	205 ± 26.6	1,230 ± 225

Mean ± standard deviation; n = 3

4.1.2 Repeated-dose study

Repeated intravenous doses of darinaparsin 5, 15, or 45 mg/kg were administered QD to male and female rats on Days 1 to 5 of each 21-day cycle, and plasma arsenic concentrations were investigated (Table 8). There were no clear differences in arsenic exposure between the sexes. Within the dose range studied, the arsenic exposure roughly increased in a dose-proportional manner on Day 1, but increased in a less than dose-proportional manner on Day 110 (Day 5 of Cycle 5). The applicant explained that the less than dose-proportional increase in arsenic exposure on Day 110 may be attributable to an increase in excretion of arsenic due to saturation of binding of dimethyl arsinous acid, a metabolite of darinaparsin, to hemoglobin, as the number of doses increased and as the dose level increased. The arsenic exposure on Day 110 was higher than that on Day 1.

Table 8. PK parameters* of arsenic (male and female rats, 18-week repeated-dose intravenous administration)

Measurement Day	Dose (mg/kg)	C_{max} (ng/mL)		AUC_{24h} (ng·h/mL)	
		Male	Female	Male	Female
Day 1	5	159.7	175.0	1,369	1,284
	15	572.4	667.1	3,300	3,037
	45	3,024	2,314	10,122	7,559
Day 110	5	3,392	1,850	46,658	21,760
	15	3,557	3,707	52,144	34,160
	45	11,093	14,422	50,267	54,179

*, PK parameters were calculated based on mean values (n = 4) of plasma darinaparsin concentrations at each time point.

4.2 Distribution

4.2.1 Tissue distribution

A single intravenous dose of ^{76}As-labeled darinaparsin 30 μCi was administered to male and female albino rats to investigate tissue distribution of radioactivity. Radioactivity concentrations in blood were higher than those in tissue. Radioactivity concentrations were particularly high in the spleen and lung (radioactivity concentrations at 0.5-48 hours post-dose were 4.87%ID/g-5.34%ID/g in blood, 0.99%ID/g-1.20%ID/g in the spleen, and 0.59%ID/g-0.84%ID/g in the lung[7)]). At 48 hours post-dose, the total of radioactivity in all the tissues examined accounted for 5.48% of radioactivity administered.

7) The blood or tissue radioactivity concentration expressed as the percentage of injected dose per weight of blood or tissue.

4.2.2 Plasma protein binding

Rat, dog, and human plasma was incubated with darinaparsin (0.55-55.5 μg/mL[8)]) at 37°C for 30 minutes, and the plasma protein binding of arsenic was determined by the ultrafiltration method.[9)] The plasma protein binding of arsenic was 78.2% to 93.5% in rats, 8.73% to 29.9% in dogs, and 78.3% to 82.9% in humans.

Rat, dog, and human plasma was incubated with dimethylarsinic acid (0.184-18.4 μg/mL) at 37°C for 30 minutes, and the plasma protein binding of dimethylarsinic acid was determined by the ultrafiltration method. Dimethylarsinic acid did not bind to rat or human plasma proteins, while in dog plasma, protein binding of dimethylarsinic acid (0.184 μg/mL[10)]) was 1.01%.

4.2.3 Distribution in blood cells

Rat, dog, and human blood was incubated with darinaparsin (0.55-55.5 μg/mL[11)]) at 37°C for 30 minutes, and the distribution of arsenic in blood cells was investigated. The blood-to-plasma arsenic concentration ratios ranged from 1.53 to 6.41 in rats, 8.60 to 10.8 in dogs, and 5.53 to 7.00 in humans. The applicant explained that the above results showed that darinaparsin-derived arsenic compounds are distributed in blood cells.

4.2.4 Placental and fetal transfer

Neither the placental nor fetal transfer of darinaparsin has been studied. Since studies have reported that inorganic arsenic crossed the placenta to the fetus (e.g., *Acta Pharmacol Toxicol.* 1984;54:311-20), the applicant explained that following administration of darinaparsin, arsenic compounds may cross the placenta and may be transported to the fetus.

4.3 Metabolism

4.3.1 *In vivo*

A single intravenous dose of darinaparsin 30 mg/kg was administered to male dogs to investigate metabolites in plasma, urine, and feces. Mainly dimethylarsinic acid was detected at 8 hours post-dose in plasma, up to 48 hours post-dose in urine, and up to 24 hours post-dose in feces, accounting for 99.4% (plasma), 99.9% (urine), and 83.9% (feces) of the total arsenic in the sample.[12)] Unchanged darinaparsin was detected (0.0658%) in plasma immediately before the end of infusion, while unchanged darinaparsin was not detected in plasma at 1, 4, and 8 hours post-dose. The applicant explained that these findings demonstrated that darinaparsin is labile in the body.

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8) The protein binding of arsenic in rats and humans was calculated based on the data for darinaparsin 2.75 to 55.5 μg/mL.
9) After incubation of rat, dog, and human plasma with darinaparsin 5.5 μg/mL at 37°C for 0 to 60 minutes, darinaparsin was not detected. Therefore, plasma binding of arsenic was studied.
10) Plasma protein binding did not occur at other concentrations (1.84 and 18.4 μg/mL).
11) The blood-to-plasma arsenic concentration ratios in dogs and humans were calculated based on the data for darinaparsin 5.5 and 55.5 μg/mL.
12) The percentage of peak area for each metabolite to the total peak area for arsenic in the chromatogram obtained through separation of a sample by liquid chromatography.

4.3.2 *In vitro*

The applicant explanation:

The investigation results below and other data suggest that metabolizing enzymes are not involved in formation of dimethylarsinic acid from darinaparsin.

- Human hepatocytes were incubated with darinaparsin (10 μmol/L) at 37°C for 4 hours in the presence of glutathione to investigate the metabolites of darinaparsin. Main metabolites detected were dimethylarsinic acid, dimethylmonothio arsinic acid, and S-(dimethylarsino)-L-cystein, which accounted for 59.3%, 14.5%, and 2.54% of the total arsenic in the sample,[12)] respectively. Dimethylarsinic acid was detected (44.2%) almost immediately after the addition of darinaparsin.
- Krebs-Henseleit buffer was incubated with darinaparsin (10 μmol/L) at 37°C for 4 hours in the presence of glutathione to investigate the stability of darinaparsin. Main metabolites detected were dimethylarsinic acid, unchanged darinaparsin, and dimethylarsinothioyl glutathione, which accounted for 68.5%, 28.9%, and 2.04% of the total arsenic in the sample, respectively. Dimethylarsinic acid and dimethylarsinothioyl glutathione were detected almost immediately after the addition of darinaparsin, which accounted for 29.9% and 1.49% of the total arsenic in the sample, respectively.

4.4 Excretion

4.4.1 Urinary and fecal excretion

The applicant's explanation:

A single intravenous dose of darinaparsin 30 mg/kg was administered to male dogs to investigate the excretion of arsenic in urine and feces (percentage of the administered arsenic). The cumulative excretion of arsenic up to 168 hours post-dose was 92.9% in urine and 1.14% in feces. The results indicated that the arsenic compounds are primarily excreted in urine after administration of darinaparsin.

4.4.2 Excretion in breast milk

Excretion of darinaparsin in breast milk has not been studied. Since arsenic excretion in breast milk has been reported (*Biomed Res Trace Elements*. 2002;13:149-57), the applicant explained that arsenic compounds may be excreted into breast milk following administration of darinaparsin.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

In addition to the evaluation results below, given that darinaparsin was not detected in the plasma of patients who received the proposed dosage regimen of darinaparsin [see Section 6.2.2.1], it is unlikely that pharmacokinetic interactions will occur through the inhibition of cytochrome P450 (CYP) isoforms by darinaparsin and dimethylarsinic acid in the clinical setting.

- Human liver microsomes were incubated with darinaparsin or dimethylarsinic acid (both at 2-

200 μmol/L) in the presence of the substrate[13)] for each CYP isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to investigate inhibition of CYP isoforms by darinaparsin or dimethylarsinic acid. Darinaparsin inhibited the metabolism of the substrates for CYP1A2 (IC_{50} = 54.2 μmol/L), CYP2C8 (IC_{50} = 16.2 μmol/L), and CYP3A (IC_{50} = 72.5 μmol/L[14)]). However, darinaparsin did not show a clear inhibitory effect on the metabolism of substrates for the other CYP isoforms tested. Dimethylarsinic acid showed no clear inhibitory effect on the metabolism of substrates for any of the CYP isoforms tested.

- Human liver microsomes were preincubated with darinaparsin (2-400 μmol/L[15)]) in the presence of NADPH, followed by incubation with substrates[13)] for CYP2B6, CYP2C9, and CYP2C19, to investigate time-dependent inhibition of CYP isoforms by darinaparsin (apparent inhibitor concentration at 50% of maximum inhibition rate [$K_{I, app}$] and maximum inactivation rate constant [k_{inact}] were obtained). Darinaparsin inhibited the metabolism of the substrates for CYP2B6 ($K_{I, app}$ = 32.3 μmol/L, k_{inact} = 0.0390 min^{-1}), CYP2C9 ($K_{I, app}$ = 403 μmol/L, k_{inact} = 0.0985 min^{-1}), and CYP2C19 ($K_{I, app}$ = 117 μmol/L, k_{inact} = 0.0464 min^{-1}) in a time-dependent manner.

4.5.2 Enzyme induction

Human hepatocytes were incubated in the presence of darinaparsin (0.2-2 μmol/L) or dimethylarsinic acid (0.2-20 μmol/L[16)]) for 72 hours, and messenger ribonucleic acid (mRNA) expression levels of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4) were analyzed. Darinaparsin (2 μmol/L) induced the mRNA expression of CYP2B6, CYP2C9, and CYP3A4, corresponding to 2.10- to 2.39-fold, 1.33- to 2.07-fold, and 1.28- to 5.09-fold, respectively, compared with the mRNA expression level of vehicle control.[17)] However, darinaparsin showed no obvious inductive effect on the mRNA expression levels of CYP1A2 or CYP2C8. On the other hand, dimethylarsinic acid (6[16)] or 20 μmol/L) induced the mRNA expression of CYP2B6, CYP2C8, and CYP3A4, corresponding to 2.01- to 3.07-fold, 1.78- to 2.71-fold, and 1.30- to 2.48-fold, respectively, compared with the mRNA expression level of vehicle control.[17)] However, dimethylarsinic acid showed no obvious inductive effect on the mRNA expression levels of CYP1A2 or CYP2C9. In addition to the above evaluation results, darinaparsin was not detected in plasma of patients who received the proposed dosage regimen of darinaparsin [see Section 6.2.2.1], and the expected C_{max} of dimethylarsinic acid at steady state for the proposed dosage regimen of darinaparsin is 17.5 μmol/L.[18)] The applicant explained that based on these

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13) The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), bupropion (CYP2B6), paclitaxel (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), and bufuralol (CYP2D6); midazolam and testosterone as substrates for CYP3A.

14) This is the IC_{50} when midazolam was used as the substrate for CYP3A; the IC_{50} was 160 μmol/L when testosterone was used.

15) The assays were conducted at concentrations 2 to 200 μmol/L (CYP2B6), 25 to 400 μmol/L (CYP2C9), and 2 to 100 μmol/L (CYP2C19).

16) Some of the assays that used hepatocytes from one donor were performed in a concentration range of 0.2 to 6 μmol/L.

17) 0.1% dimethyl sulfoxide (DMSO) was used as the vehicle control.

18) The value was calculated based on the C_{max} in Japanese patients on Day 5 following intravenous administration of darinaparsin 300 mg/m^2 on Days 1 to 5 [see Section 6.2.8] in the global phase II study (Study 02), and the percentage of dimethylarsinic acid of the total arsenic in plasma (approximately 90%) [see Section 6.2.2.1].

factors, pharmacokinetic interactions through the induction of CYP2B6, CYP2C8, and CYP3A4 by dimethylarsinic acid are likely to occur in the clinical use of darinaparsin.

4.5.3 Transporters

The applicant's explanation:

The following study results demonstrated that neither darinaparsin nor dimethylarsinic acid are substrates for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, and organic cation transporter (OCT)2.

- Using the human colon cancer Caco-2 cell line, P-gp or BCRP-mediated transport of darinaparsin and dimethylarsinic acid (both at 10 μmol/L) was investigated. The results showed an efflux ratio of <2 for darinaparsin, and no transport of dimethylarsinic acid.
- Using HEK293 cells expressing human OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, the transport of darinaparsin and dimethylarsinic acid (both at 10 μmol/L) mediated by each transporter was investigated. The ratios of the uptake rate for transporter-expressing cells to the uptake rate of transporter non-expressing cells for darinaparsin were all <2. In contrast, uptake of dimethylarsinic acid was not observed in any of the transporter-expressing cells.

The applicant explained that, in addition to the evaluation results below, given that darinaparsin was not detected in the plasma of patients who received the proposed dosage regimen of darinaparsin [see Section 6.2.2.1], pharmacokinetic interactions through the inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 by darinaparsin and dimethylarsinic acid are unlikely to occur in the clinical use of darinaparsin.

- Using Caco-2 cell line, the inhibitory effects of darinaparsin and dimethylarsinic acid (both at 1-300 μmol/L) on the transport of substrates[19)] for P-gp and BCRP were investigated. Darinaparsin inhibited the transport of the substrate for P-gp (IC_{50} = 133 μmol/L). Darinaparsin did not show a clear inhibitory effect on the transport of the substrate for BCRP. Dimethylarsinic acid showed no clear inhibitory effect on the transport of substrates for P-gp and BCRP.
- Using HEK293 cells expressing human OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, the inhibitory effects of darinaparsin and dimethylarsinic acid (both at 1-300 μmol/L) on the transport of substrates[20)] were investigated. Neither darinaparsin nor dimethylarsinic acid showed a clear inhibitory effect on the transport of substrates for any of the transporters.

19) ^{3}H-labeled digoxin (1 μmol/L) and ^{3}H-labeled estrone-3-sulfate (1 μmol/L) were used as the substrates for P-gp and BCRP, respectively.

20) The following radiolabeled compounds were used as the substrates for the transporters: ^{3}H-labeled estrone-3-sulfate (0.005 μmol/L) for OATP1B1, ^{3}H-labeled estradiol 17β-D-glucuronide (1 μmol/L) for OATP1B3, ^{3}H-labeled *p*-aminohippuric acid (3 μmol/L) for OAT1, ^{3}H-labeled estrone-3-sulfate (2 μmol/L) for OAT3, and ^{3}H-labeled metformin (120 μmol/L) for OCT2.

4.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about non-clinical pharmacokinetics is acceptable.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about the pharmacokinetic interactions mediated by metabolizing enzymes (CYP2B6, CYP2C8, and CYP3A4):

The *in vitro* test results suggested that dimethylarsinic acid may cause pharmacokinetic interactions through the induction of CYP2B6, CYP2C8, and CYP3A4 [see Section 4.5.2]. However, there were no particular safety concerns associated with the use of darinaparsin in combination with the substrates for CYP2B6, CYP2C8, and CYP3A in the Japanese phase I study (Study 01), global phase II study (Study 02), and foreign phase I study (Study 03). The findings and other data indicated that darinaparsin is unlikely to cause problems when used in combination with these substrates in clinical use.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, information on the pharmacokinetic interactions of dimethylarsinic acid through CYP2B6, CYP2C8, and CYP3A is important for the proper use of darinaparsin. Therefore, the applicant should continue to collect relevant information, and any useful information should be provided to healthcare professionals in an appropriate manner when it becomes available.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Although no single-dose toxicity studies were conducted, the acute toxicity of darinaparsin was evaluated in the 4-week repeated intravenous dose toxicity study in rats, 5-day repeated intravenous dose toxicity study in mice, mouse micronucleus assay, and 4-week and 18-week repeated intravenous dose toxicity studies in dogs. In rats, there were deaths at ≥50 mg/kg, with main acute symptoms including tachypnea, flush, and oedema. In mice, main acute symptoms were decrease in locomotor activity in the 5-day repeated intravenous dose toxicity study (CTD 4.2.3.2.1), and incomplete eyelid opening, oral discharge, and ataxia in the micronucleus assay, in which a single intravenous dose was administered [see Section 5.3]. In dogs, there were no deaths, and acute symptoms suspected to have been the effect of darinaparsin on the central nervous system included hyperexcitation, discomfort, jumping, fall, unusual locomotion, prostration, lethargy, emesis/nausea, and fasciculation. The applicant explained that the approximate lethal dose for intravenous administration of darinaparsin was 50 mg/kg in rats and >30 mg/kg in dogs based on the above findings.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in rats and dogs (4 weeks and 18 weeks) (Table 9). Main toxicity findings in rats were death due to worsened clinical signs, and inhibition of testicular spermatogenesis; while those in dogs were abnormal clinical signs similar to acute symptoms of arsenic

exposure, QTc interval prolongation, and testicular spermatid retention. In the 18-week repeated-dose study in rats, low percentage of bone-marrow lymphocyte series and high percentage of bone-marrow granulocyte series were reported, and in the 18-week repeated-dose study in dogs, abnormal clinical signs were reported at 3 mg/kg. The applicant explained that these findings were not considered to be toxicities because of absence of associated changes or sporadic occurrence.

In the 18-week repeated-dose studies in rats and dogs, arsenic exposures in blood (AUC_{24h}) at the no-observed adverse effect level (NOAEL) were 52,144 ng·h/mL (male rats), 34,160 ng·h/mL (female rats), 2,798 ng·h/mL (male dogs), and 2,680 ng·h/mL (female dogs). These exposures were approximately 2.2 times (male rats), 1.4 times (female rats), and 0.1 times (male and female dogs) the arsenic exposures in blood at the recommended clinical dose.[21)]

Table 9. Repeated-dose toxicity studies

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male/female rats (Sprague Dawley)	IV	4 weeks: 7 days (QD) on treatment + 7 days off treatment, repeated for 2 cycles	0,[*1] 30, 50, 75	<u>Died[*2]</u> At 50, 3 of 3 females At 75, 2 of 3 males, 3 of 3 females Salivation, flush, tachypnea, abnormal respiration, gasping, weak breathing, coarse fur, loose stool, soiled perineal region, decrease in locomotor activity, nasal discharge, oedema in the nose/ankle, prostration, lethargy, lacrimation, emaciation, scab at the administration site, blackening/yellow region in the liver peripheral zone, pale discoloration of the pancreas, retention of light yellow jelly-like material in the digestive tract, gastric dilatation, thinning of stomach/small intestinal walls, dark reddening of the adrenal gland, reduced thymus/spleen size <u>Surviving animals</u> At ≥30, salivation (males/females); low body weight gain, low food consumption (males) At ≥50, tachypnea, flush (males/females); low food consumption (females) At 30, wound/scab at the administration site, broken tail, reduced spleen size (males) At 50, abnormal respiration, oedema in the nose/ankle (males); low body weight, low body weight gain (females) At 75, coarse fur (males)	<30	4.2.3.2.3

[21)] In the global phase II study (Study 02), the arsenic exposure in blood (AUC_{24h}) on Day 5 was 24,006 ng·h/mL following intravenous administration of darinaparsin 300 mg/m^2 on Days 1 to 5 [see Section 6.2.2.1].

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male/female rats (Sprague Dawley)	IV	18 weeks: 5 days (QD) on treatment + 16 days off treatment, repeated for 6 cycles, 4-week recovery period	0,[*1] 5, 15, 45	<u>Died[*2]</u> At 45, 2 of 15 females[*3] hyperexcitation, circling, lethargy, hunched back, salivation, lacrimation, eye discharge, nasal discharge, flush, loose stool, soiled perineal region, coarse fur, oedema/scab/ulceration/color fading/inflammation/necrosis at the administration site, broken tail <u>Surviving animals</u> At ≥5, bone-marrow lymphocyte series low percentage, bone-marrow granulocyte series high percentage[*4] (males) At 45, low body weight gain/low food consumption, hyperexcitation, circling, lacrimation, salivation, loose stool, oedema in the tail, flush, tail ulceration/scab, soiled perineal region, coarse fur, loss of tail, high reticulocyte count (males/females); low body weight, color fading of the tail, desquamation, low epididymal weight, low testicular weight, epididysmal luminal cell debris/decreased sperm count in the duct of epididysmis, degeneration/atrophy of seminiferous tubules/degeneration of elongated spermatids (males); hunched back, rough fur, pale (females) Reversibility: reversible	15	4.2.3.2.5
Male/female dogs (Beagle)	IV	4 weeks: 7 days (QD) on treatment + 7 days off treatment, repeated for 2 cycles	0,[*1] 5, 15, 25	At ≥15, salivation, spitting froth, lacrimation, flush, conjunctival congestion (males/females); unusual locomotion, hyperexcitation or discomfort, pruritus (males) At 25, jumping or fall (males/females); prostration (males); hyperexcitation or discomfort, unusual locomotion, nausea, emesis, fasciculation, loose stool, or watery stool (females)	5	4.2.3.2.4
Male/female dogs (Beagle)	IV	18 weeks 5 days (QD) on treatment + 16 days off treatment, repeated for 6 cycles, 4-week recovery period	0,[*1] 3, 10, 30	At ≥3, hyperexcitation, unusual locomotion, eyelid swelling/redness,[*5] flush, conjunctival congestion, salivation, oedema at the administration site, increased heart rate (males/females); loose stool (males); pruritus (females) At ≥10, lethargy, prostration, lacrimation, eye discharge,[*6] emesis (males/females); testicular spermatid retention (males); QTc interval prolongation (females) At 30, quivering/shivering, spitting froth (males/females); nasal discharge, bloody stool, pruritus (males); fasciculation, loose stool (females) After recovery period,[*7] At 30, testicular spermatid retention	3	4.2.3.2.6

*1, physiological saline; *2, only main toxicity findings associated with darinaparsin treatment are shown; *3, deaths in the toxicokinetics (TK) group are excluded; *4, including the percentages that tend to be high; *5, females in the 3 mg/kg group are excluded; *6, males in the 30 mg/kg group are excluded; *7, only findings that are not reversible are shown

5.3 Genotoxicity

Genotoxicity studies consisted of a bacterial reverse mutation assay (Ames test), a chromosomal aberration assay in mammalian cells, and a mouse micronucleus assay (Table 10). The applicant explained that darinaparsin is mutagenic under metabolically activated conditions.

Table 10. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration or dose	Test result	CTD
In vitro	Ames test	*Salmonella* Typhimurium: TA98, TA100, TA1535	S9−/+	0,* 6, 13, 25, 50, 100, 250 μg/plate	Negative	4.2.3.3.1.1
		Salmonella Typhimurium: TA1537	S9−/+	0,* 6, 13, 25, 50, 100, 250 μg/plate	Positive (S9+)	
		Escherichia coli: WP2*uvrA*	S9−	0,* 6, 13, 25, 50, 100, 250 μg/plate	Negative	
			S9+	0,* 19, 38, 75, 150, 300, 500 μg/plate	Positive	
	Chromosomal aberration assay	Human peripheral blood lymphocytes	S9− (24 hours)	0,* 6.00, 8.58, 12.3 μg/mL	Positive Structural aberration	4.2.3.3.1.2
			S9+ (24 hours)	0,* 12.3, 17.5, 25.0 μg/mL	Positive Structural aberration	
In vivo	Micronucleus assay	Male mice (CD-1), single-dose, IV, bone marrow		0,* 40, 80, 160 mg/kg	Negative	4.2.3.3.2.1

*, Physiological saline

5.4 Carcinogenicity

No carcinogenicity studies were conducted because darinaparsin is an antineoplastic agent intended to be used for the treatment of patients with advanced cancer.

5.5 Reproductive and developmental toxicity

In the repeated-dose toxicity study in rats, a change in testicular spermatogenesis was observed after administration of darinaparsin [see Section 5.2]. An embryo-fetal development study was conducted in pregnant rabbits. Embryo lethality and decrease in the number of live fetuses were observed among the main toxicity findings for embryos and fetuses (Table 11). The arsenic exposure in blood (AUC_{24h}) at the NOAEL for rabbit embryos/fetuses (10 mg/kg) was 9,393 ng·h/mL, approximately 0.4-times the arsenic exposure in blood at the recommended clinical dose.[21)]

Table 11. Reproductive and developmental toxicity study

Type of study	Test system	Route of adminis-tration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Embryo-fetal development	Female rabbits (New Zealand White)	IV	Gestation Days 6-18 (QD)	0,* 3, 10, 30	Dams <u>Died</u> At 10, 1 of 24 animals At 30, 5 of 24 animals Miosis, lacrimation, salivation, hyperexcitation, reduced/lack of defecation, low food consumption <u>Surviving animals</u> At ≥10, hyperexcitation, lacrimation, miosis, salivation, oedema/discoloration/flush/scab/ fever/ulceration/darkening of the administration site At 30, lethargy, reduced/lack of defecation, high number of abortions, low body weight gain, low food consumption, abortion, low uterus weight Embryos/fetuses At 30, low implantation rate, high pre-and post-implantation losses, high total number and rate of resorption, high number/rate of early resorption, low rate/number of fetal survival	Parent animals, 3 Embryos/ fetuses, 10	4.2.3.5.2.2

*, Physiological saline

5.6 Local tolerance

Local irritation of darinaparsin was evaluated based on the clinical observation of the administration site, as well as the findings from necropsies and histopathological studies in the repeated intravenous dose toxicity studies in rats and dogs [see Section 5.2]. After intravenous administration, oedema, wounds, scabbing or ulceration, inflammation, necrosis, and other findings were observed at the administration site in rats, while oedema was observed in dogs. Darinaparsin was determined to be a local irritant based on the observed results. In addition, administration site anomalies occurred following administration through a peripheral vein in the clinical studies. The applicant considers that it is advisable to administer darinaparsin via a central vein due to these reasons, and this information will be provided to healthcare professionals in an appropriate manner using the package insert or other materials [see Section 7.R.5.3].

5.7 Other toxicity studies

5.7.1 Photosafety

A neutral red uptake phototoxicity test was conducted using mouse fibroblasts (Table 12). The applicant explained that darinaparsin is not phototoxic.

Table 12. Photosafety study

Test system	Test method	Main findings	CTD
Mouse fibroblasts (Balb/c 3T3)	0,* 1.125, 2.25, 4.5, 9, 18, 36, 72, and 144 μg/mL Cells are irradiated with UVA (5 J/cm^2) for 50 minutes	PIF: 2.185, MPE: 0.032 Not phototoxic	4.2.3.7.7.1

*, Earle's balanced salt solution

5.7.2 Safety evaluation of impurities

The safety of Impurity A, Impurity B, Impurity C, and Impurity D contained in the drug substance and drug product was evaluated. In the 15-week repeated-dose toxicity study in rats, general toxicity was studied by using the drug substance containing 1% of Impurity A. The results showed no toxicity findings associated with Impurity A (Table 13). The maximum exposures to Impurity B and Impurity C do not exceed the maximum daily dose level of an intravenous formulation of [redacted] ([redacted][22]), which has already been approved in Japan; therefore, the applicant explained that these impurities are unlikely to lead to safety concerns. Impurity D is a decomposition product/metabolite that is detected after administration of darinaparsin both in human and in animal studies. The applicant explained that exposure to Impurity D contained in the drug substance and drug product is considered to be well-tolerated in patients with cancer.

Table 13. General toxicity study of impurity

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main finding	CTD
Male/female rats (Sprague Dawley)	IV	15 weeks: 5 days on treatment (QD) + 16 days off treatment, repeated for 5 cycles, 4-week recovery period	0,*1 15*2	There were no toxicity findings resulting from the impurity	4.2.3.7.6.1

*1, Physiological saline; *2, containing 1% of Impurity A

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about the toxicity of darinaparsin is acceptable.

5.R.1 Effects on the central nervous system

Acute symptoms that are suspected to be the effect of darinaparsin on the central nervous system were observed in the repeated-dose toxicity study in dogs [see Sections 5.1 and 5.2]. The applicant's explanation about the mechanism of these symptoms and whether they are tolerable by humans:

Although the mechanisms of the above findings are unknown, similar findings have been reported as acute symptoms caused by arsenic compounds (*Initial Risk Assessment Report on Chemical Substances*), thus suggesting the effect of arsenic exposure. Additionally, adverse events relating to nervous system disorder have been reported at a certain frequency after administration of darinaparsin in clinical studies [see Section 7.R.3.5]; therefore, information on central nervous system disorders will be provided to healthcare professionals in an appropriate manner using the package insert and other materials.

22) Because [redacted], both substances were considered to have comparable biological effects, and it was concluded that the human dose level of the approved formulation of [redacted] can be used for safety evaluation.

PMDA accepted the applicant's explanation.

Effects on the central nervous system in humans will be discussed in Section "7.R.3.5 Nervous system disorders."

5.R.2 Effects on spermatogenesis

The applicant's explanation about the effects of toxicity on male reproductive organs relating to disorders of spermatogenesis observed in the repeated-dose toxicity studies in mice, rats, and dogs:
Since the data from the repeated-dose toxicity studies showed that male reproductive organs are the target organs of toxicity associated with darinaparsin, the possibility that darinaparsin may affect the male reproductive organs cannot be ruled out. Therefore, the applicant plans to caution healthcare professionals regarding the effects of darinaparsin on the male reproductive organs in the package insert and other materials.

PMDA accepted the applicant's explanation.

5.R.3 Use of darinaparsin in pregnant women, women who may be pregnant, or nursing women

The applicant's explanation about the use of darinaparsin in pregnant women, women who may be pregnant, or nursing women based on the results of the embryo-fetal development studies of darinaparsin [see Section 5.5] and knowledge on the effects of arsenic on reproduction, development, and other factors:
Darinaparsin should be contraindicated in pregnant women or women who may be pregnant because the possibility of maternal and fetal toxicity cannot be ruled out given that findings including abortion and reduced number of live fetuses have been reported in the embryo-fetal development study of darinaparsin in rabbits, even though its teratogenic effect has not been demonstrated.

In Japan, there was an incident of arsenic poisoning caused by contamination of dry milk formula with arsenic compounds, which resulted in death of infants as well as skin symptoms (*Initial Risk Assessment Report on Chemical Substances*). A cautionary statement to the effect that mothers should avoid breastfeeding during treatment with darinaparsin will be included in the package insert or other materials to alert healthcare professionals in an appropriate manner for the following reasons: (1) excretion of darinaparsin in human breast milk has not been observed; however, arsenic compounds may be excreted in breast milk following administration of darinaparsin [see Section 4.4.2]; (2) the effect of excessive exposure to arsenic in infant through the mother's breast milk after administration of darinaparsin is unclear, and safety concerns cannot be denied.

PMDA' discussion:
Darinaparsin is one of the metabolic intermediates formed in the *in vivo* metabolic process of inorganic arsenic compounds. It has been reported that excessive long-term consumption of arsenic by humans may have harmful effects on reproduction and development such as increases in abortion and stillbirth

risk (*Int. J. Environ. Health Res.* 2004;14:99-108). Taking into account of these and other factors, PMDA concluded that the applicant's explanation above is acceptable.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Assays of arsenic in human plasma and urine were conducted by inductively coupled plasma mass spectrometry, with a lower limit of quantitation of 50 and 500 ng/mL, respectively.

6.2 Clinical pharmacology

The PK of arsenic[6)] in patients with cancer is evaluated when darinaparsin alone was administered.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2.1, Study 01 [February 2012 to April 2015)

An open-label, uncontrolled study was conducted in 17 patients (17 subjects in the PK analysis set) with relapsed or refractory PTCL to investigate arsenic PK and other parameters after administration of darinaparsin. Intravenous doses of darinaparsin 200 or 300 mg/m^2 were administered over approximately 1 hour on Days 1 to 5 in 21-day or 28-day cycles,[23)] and plasma arsenic concentrations were evaluated.

Table 14 shows PK parameters of arsenic. The Day 5 to Day 1 AUC_{24h} ratio was 1.7 at darinaparsin 300 mg/m^2. The plasma arsenic concentrations on Day 15 were below the lower limit of quantitation at both dose levels.

Table 14. PK parameters of arsenic

Dose (mg/m^2)	Treatment	n	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{1/2}$*1 (h)
200	Day 1	3	688 ± 116	8,728 ± 1,893	15 ± 2.6
	Day 5	3	884 ± 74	13,130 ± 2,575	16 ± 1.9
300*2	Day 1	14	838 ± 180	12,759 ± 3,419	20 ± 6.3
	Day 5	14	1,314 ± 333	21,236 ± 6,004	21 ± 5.8

Mean ± standard deviation; *1, calculated using data up to 24 hours post-dose on Day 1, and up to 72 hours post-dose on Day 5; *2, PK parameters at 300 mg/m^2 are combined results from Cohorts 2 and 3

6.2.2 Global clinical study

6.2.2.1 Global phase II study (CTD 5.3.5.2.1, Study 02 [March 2016 to June 2021])

An open-label, uncontrolled study was conducted in 67 patients (44 subjects in the PK analysis set) with relapsed or refractory PTCL to investigate arsenic PK and other parameters after administration of darinaparsin. Intravenous doses of darinaparsin 300 mg/m^2 were administered over approximately 1 hour on Days 1 to 5 in 21-day cycles, and arsenic concentrations in plasma and urine were evaluated. Metabolites in plasma and urine on Day 5 were evaluated in 17 subjects.

[23)] Each cycle consisted of 28 days in Cohort 1 (200 mg/m^2) and Cohort 2 (300 mg/m^2), and 21 days in Cohort 3 (300 mg/m^2).

Table 15 shows PK parameters of arsenic. On Day 5, mainly dimethylarsinic acid was detected both in plasma at 1 to 4 hours post-dose, and in urine up to 24 hours post-dose, accounting for 91.8% and >99%[24] of the total arsenic in the sample,[12] respectively. Unchanged darinaparsin was not detected.

Table 15. PK parameters of arsenic

Treatment	n	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)	Fe[*1] (%)
Day 1	43	852 ± 204	13,976 ± 3,235	—	40.8 ± 15.3[*2]
Day 5	41	1,359 ± 368	24,006 ± 9,064	25.1 ± 9.3[*3]	67.7 ± 18.6[*4]

Mean ± standard deviation; *1, urinary excretion rate of arsenic up to 24 hours post-dose on Day 1 or Day 5; *2, n = 44; *3, n = 40; *4, n = 39; "—," not calculated

6.2.3 Foreign clinical study

6.2.3.1 Foreign phase I study (CTD 5.3.3.2.4, Study SGL1002 [July 2005 to July 2007])

An open-label, uncontrolled study was conducted in 41 patients with advanced solid tumors (38 subjects in the PK analysis set) to investigate arsenic PK and other parameters after administration of darinaparsin. Intravenous doses of darinaparsin 78 to 588 mg/m^2 were administered over approximately 1 hour on Days 0 to 4 in 28-day cycles, and arsenic concentrations in plasma were evaluated.

Table 16 shows PK parameters of arsenic after the first dose of darinaparsin.

Table 16. PK parameters of arsenic

Dose (mg/m^2)	n	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)
78	3	238 ± 23	4,338 ± 1,225	20.0 ± 6.8
109	3	325 ± 17	5,071 ± 353	16.0 ± 4.6
153	5	402 ± 33	6,021 ± 860	15.1 ± 3.1
214	3	603 ± 170	9,039 ± 2,641	15.1 ± 1.3
300	6	738 ± 134	10,311 ± 1,950	16.3 ± 4.9
420	11	1,011 ± 221	15,604 ± 3,790	17.6 ± 6.2
500	3	1,049 ± 73	16,310 ± 3,159	20.6 ± 9.0
588	4	1,468 ± 250	25,623 ± 7,155	23.3 ± 9.0

Mean ± standard deviation

6.2.4 Use of darinaparsin in patients with hepatic impairment

No clinical studies were conducted in patients with hepatic impairment to investigate the effects of hepatic impairment on PK parameters of arsenic following administration of darinaparsin.

The applicant explained that dose adjustment of darinaparsin is unnecessary for patients with hepatic impairment based on various factors including the following:

- Hepatic metabolism is considered to have a limited contribution to elimination of darinaparsin based on the results from *in vitro* studies and the global phase II study (Study 02) [see Sections 4.3.2 and 6.2.2.1].
- In the Japanese phase I study (Study 01), global phase II study (Study 02), and foreign phase I study

[24] There were no clear differences between time points in the percentage of each metabolite in the total arsenic in plasma and in urine; therefore, the mean values for each time point are presented (at 1, 2, and 4 hours post-dose for plasma; 0-4 hours and 4-24 hours post-dose for urine).

(Study 03), the incidence of adverse events was studied in patients with normal hepatic function (n = 78) and patients with mild hepatic impairment[25] (n = 10). The incidence of Grade ≥3 adverse events was 60.3% (normal) and 70.0% (mild impairment), and the incidence of serious adverse events was 41.0% (normal) and 60.0% (mild impairment), indicating that the incidences in patients with normal hepatic function did not differ clearly from those in patients with mild hepatic impairment.

6.2.5 Relationship between exposure and change in QT/QTc interval

On the basis of the results from the Japanese phase I study (Study 01) and foreign phase I study (Study 03), the relationship between plasma arsenic concentration and change from baseline in QT interval corrected with Fridericia's formula (ΔQTcF) was investigated using a simple regression model. The results indicated no clear relationship between plasma arsenic concentrations and ΔQTcF. Data on the incidence of QT interval prolongation in the clinical studies, and discussion on cautionary statements regarding QT interval prolongation based on data including the incidence will be described in Section "7.R.3.6 Cardiac disorders."

6.2.6 Patient characteristics that have an impact on PK

Patient characteristics that may affect the PK of arsenic were investigated based on the arsenic PK data at darinaparsin 300 mg/m^2 obtained from the Japanese phase I study (Study 01), global phase II study (Study 02), and foreign phase I study (Study 03).

The relationship of arsenic PK (C_{max} and AUC_{24h}) on Days 1 and 5 of darinaparsin treatment with renal function (creatinine clearance [CrCL] and estimated glomerular filtration rate [eGFR]), hepatic function (bilirubin, albumin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]), age, or body weight was evaluated. The renal function parameters (CrCL and eGFR) were identified to be related to the C_{max} and AUC_{24h} of arsenic on Days 1 and 5. Furthermore, a linear model with race, sex, and treatment day, in addition to renal function (CrCL), as covariates, was used to evaluate the effect of these covariates on the C_{max} and AUC_{24h} of arsenic. Although the C_{max} and AUC_{24h} of arsenic did not differ clearly between the races or the sexes, arsenic exposures tended to increase as the severity of renal impairment increased (the geometric mean ratio of patients with mild renal impairment to patients with normal real function with their 90% confidence interval [90% CI] for arsenic C_{max} was 1.10 [1.00, 1.21] and that for AUC_{24h} was 1.24 [1.12, 1.38]; the geometric mean ratio of patients with moderate renal impairment[26] to patients with normal real function with their 90% confidence interval for arsenic C_{max} was 1.27 [1.16, 1.41] and that for AUC_{24h} was 1.60 [1.44, 1.78]). On the basis of the arsenic PK data of the Japanese subpopulation from the above clinical studies, additional analysis was conducted using a

[25] Patients were classified according to the criteria by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG).

[26] Patients were classified based on the following definitions: "normal," CrCL (mL/min) of ≥90; "mild," ≥60 and <90; and "moderate," ≥30 and <60.

linear model with renal function (eGFR), sex, and treatment day. The results tended to be similar to those of the overall study population.

6.2.7 Relationships of exposure with efficacy and safety

On the basis of the results of the global phase II study (Study 02), the relationship of arsenic exposure with efficacy and safety was evaluated.

6.2.7.1 Relationship between exposure and efficacy

Relationship between arsenic exposure (C_{max} and AUC_{24h} on Days 1 and 5) and response[27)] was investigated. The results indicated no clear relationship between arsenic exposure and response.

6.2.7.2 Relationship between exposure and safety

Relationships between arsenic exposure (C_{max} and AUC_{24h} on Days 1 and 5) and the incidence of anaemia, decreased appetite, malaise, pyrexia, ALT increased, AST increased, and platelet count decreased were investigated. The results indicated no clear relationships between arsenic exposure and the incidence of adverse events listed above.

6.2.8 Differences in PK between the Japanese and non-Japanese populations

In the global phase II study (Study 02), when darinaparsin 300 mg/m^2 was intravenously administered, PK parameters of arsenic in Japanese patients did not differ clearly from those in non-Japanese patients (Table 17). On the basis of the results and other data, the applicant explained that there are no clear differences in PK of arsenic following administration of darinaparsin between Japanese and non-Japanese populations.

Table 17. PK parameters of arsenic

Subjects	Treatment	n	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)	Fe[*1] (%)
Japanese patients	Day 1	18	906 ± 167	15,476 ± 3,425	—	49.2 ± 10.4
	Day 5	18	1,451 ± 323	25,560 ± 7,987	22.6 ± 6.3	73.5 ± 14.4
Non-Japanese patients	Day 1	25	812 ± 222	12,897 ± 2,665	—	34.9 ± 15.6[*3]
	Day 5	23	1,288 ± 391	22,790 ± 9,825	27.1 ± 10.9[*2]	62.8 ± 20.7[*4]

Mean ± standard deviation; *1, urinary excretion rate of arsenic up to 24 hours post-dose on Day 1 or Day 5; *2, n = 22; *3, n = 26; *4, n = 21; "—," not calculated

6.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about the clinical pharmacology and other aspects of darinaparsin is acceptable.

6.R.1 Use of darinaparsin in patients with renal impairment

No clinical studies were conducted in patients with renal impairment to investigate the effects of renal impairment on PK parameters of arsenic following administration of darinaparsin.

27) Patients who were assessed as having a complete response (CR) or partial response (PR) were classified as responders, and those who were assessed as having a stable disease (SD) or progressive disease (PD) were classified as non-responders.

The applicant's explanation about the use of darinaparsin in patients with renal impairment:
Because (1) arsenic is primarily eliminated via renal excretion following administration of darinaparsin [see Section 6.2.2.1], and (2) the exposure of arsenic tended to increase with increasing severity of renal impairment in the study of patient characteristics that may have an effect on arsenic PK [see Section 6.2.6], cautionary statements will be included in the package insert to the effect that when administering darinaparsin to patients with renal impairment, dose reduction of darinaparsin should be considered as necessary, and the patient's condition should be closely monitored for development of adverse events. Using data from the Japanese phase I study (Study 01), global phase II study (Study 02), and foreign phase I study (Study 03), the incidence of adverse events was studied in patients with normal renal function (n = 29), patients with mild renal impairment (n = 32), and patients with moderate renal function (n = 26).[28)] The incidence of Grade ≥3 adverse events was 65.5% (normal), 50.0% (mild impairment), and 69.2% (moderate impairment), and the incidence of serious adverse events was 31.0% (normal), 46.9% (mild impairment), and 50.0% (moderate impairment), showing no clear relationship between the severity of renal function and incidence of adverse events.

PMDA's discussion:
Because there have been no clinical study data on the effects of renal impairment on arsenic PK, currently available evidence is insufficient to justify a cautionary statement to the effect that dose reduction of darinaparsin should be considered for patients with renal impairment. However, following administration of darinaparsin, arsenic is eliminated from the body mainly by renal excretion. For this and other reasons, healthcare professionals should pay attention when using darinaparsin for patients with renal impairment; in this regard, it is necessary to include cautionary statements in the package insert. Because information on arsenic PK in patients with renal impairment is important for proper use of darinaparsin, PMDA concluded that the applicant should continue to collect the information, and when new findings become available, the information should be provided to healthcare professionals in an appropriate manner.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

As summarized in Table 18, the applicant submitted efficacy and safety evaluation data, in the form of results data from 3 studies: 1 Japanese phase I study, 1 global phase II study, and 1 foreign phase I study. The applicant also submitted the results of 6 clinical studies (2 foreign phase I studies, 1 foreign phase I/II study, and 3 foreign phase II studies) as reference data.

28) Patients were classified based on the following definitions: "normal," CrCL (mL/min) or eGFR (mL/min/1.73m^2) of ≥90; "mild," ≥60 and <90; "moderate," ≥30 and <60; and "severe," ≥15 and <30.

Table 18. List of clinical studies on efficacy and safety

Data type	Region	Study identifier	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japanese	01	I	Patients with relapsed or refractory PTCL	17 (1) 3 (2) 7 (3) 7	In each cohort, patients received intravenous doses of darinaparsin on Days 1-5 of each cycle (maximum of 4 cycles) (1) 200 mg/m^2 (28-day cycle) (2) 300 mg/m^2 (28-day cycle) (3) 300 mg/m^2 (21-day cycle)	Safety PK
	Global	02	II	Patients with relapsed or refractory PTCL	65	Patients received intravenous doses of darinaparsin 300 mg/m^2 on Days 1-5 of each 21-day cycle (maximum of 6 cycles)	Efficacy Safety PK
	Foreign	03	I	Patients with relapsed or refractory PTCL	6 (1) 3 (2) 3	In each cohort, patients received intravenous doses of darinaparsin on Days 1-5 of each cycle (maximum of 4 cycles) (1) 300 mg/m^2 (28-day cycle) (2) 300 mg/m^2 (21-day cycle)	Safety PK
Reference	Foreign	SGL1001	I	Patients with relapsed or refractory hematopoietic malignancies	11	Patients received intravenous doses of darinaparsin 78, 109, 153, or 214 mg/m^2 on Days 1-5 of each 28-day cycle (maximum of 6 cycles)	Safety PK
		SGL1002	I	Patients with advanced solid tumors	41	Patients received intravenous doses of darinaparsin 78-588 mg/m^2 on Days 1-5 of each 28-day cycle (maximum of 6 cycles)	Safety PK
		SGL2001	I/II	Patients with refractory MM	31 (1) 17 (2) 14	(1) Phase I part: Patients received intravenous doses of darinaparsin 109-420 mg/m^2 on Days 1-5 of each 28-day cycle (maximum of 6 cycles) (2) Phase II part: Patients received intravenous doses of darinaparsin 300 mg/m^2 on Days 1-5 of each 28-day cycle (maximum of 6 cycles)	Efficacy Safety PK
		SGL2001b	II	Patients with refractory MM	17	Patients received intravenous doses of darinaparsin 420 mg/m^2 twice weekly (≥72 hours between doses) for 3 weeks followed by 1-week rest period in each 28-day cycle (maximum of 6 cycles)	Efficacy Safety
		SGL2003	II	Patients with refractory hematopoietic malignancies	50	Patients received intravenous doses of darinaparsin 300 mg/m^2 on Days 1-5 of each 28-day cycle (maximum of 6 cycles)	Efficacy Safety
		SGL2005	II	Patients with advanced hepatocellular carcinoma	15	Patients received intravenous doses of darinaparsin 420 mg/m^2 twice weekly (≥72 hours between doses) for 3 weeks followed by 1-week rest period in each 28-day cycle (maximum of 6 cycles)	Efficacy Safety

The following sections provide an outline of the clinical studies. Main adverse events other than deaths that occurred in the clinical studies are described in Section "7.3 Adverse events and other findings reported in clinical studies," while PK-related results from the studies are summarized in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2.1, Study 01 [February 2012 to April 2015])

An open-label, uncontrolled study was conducted at 4 study centers in Japan to assess various aspects of darinaparsin including safety and PK in patients with relapsed or refractory PTCL (target sample size, 15 subjects in total; 3 subjects in Cohort 1, 6 subjects in Cohort 2, and 6 subjects in Cohort 3).

The dosage regimens were as follows: in Cohort 1, darinaparsin 200 mg/m^2 on Days 1 to 5 in 28-day cycles; in Cohort 2, darinaparsin 300 mg/m^2 on Days 1 to 5 in 28-day cycles; and in Cohort 3, darinaparsin 300 mg/m^2 on Days 1 to 5 in 21-day cycles. Darinaparsin was administered as intravenous infusion over approximately 1 hour. Subjects were to continue treatment up to 4 cycles unless disease progression or the treatment discontinuation criteria were met.[29)]

All 17 subjects enrolled in the study (3 in Cohort 1, 7 in Cohort 2, and 7 in Cohort 3) received darinaparsin. These subjects were included in the safety analysis set and evaluated for dose limiting toxicity (DLT).

In the first cycle, which was defined as the DLT assessment period (for 28 days after the start of darinaparsin treatment in Cohorts 1 and 2; for 21 days after the start of darinaparsin treatment in Cohort 3), DLT was observed in 1 of 7 subjects in Cohort 3 (Grade 3 hepatic function abnormal), and maximum tolerated dose (MTD) was not determined.

No deaths were reported during the treatment period of darinaparsin and within 28 days of the end of treatment.

7.1.2 Global study

7.1.2.1 Global phase II study (CTD 5.3.5.2.1, Study 02 [March 2016 to June 2021])

An open-label, uncontrolled study was conducted at 25 study centers in 4 countries/regions including Japan to assess the efficacy, safety, and PK of darinaparsin in patients with relapsed or refractory PTCL (target sample size, 65 subjects).

Doses of darinaparsin 300 mg/m^2 were administered as intravenous infusion over approximately 1 hour on Days 1 to 5 in 21-day cycles. Subjects were to continue treatment up to 6 cycles until disease progression or the treatment discontinuation criteria were met.[30)]

Of 67 subjects enrolled in the study, 65 subjects[31)] received darinaparsin, and were included in the safety analysis set (37 Japanese subjects were included). Of the subjects who received darinaparsin, those who met the inclusion criteria and received ≥1 antitumor response assessment after the start of treatment with

29) If the patient wishes to continue receiving darinaparsin, and the investigator considers that the continuation of darinaparsin is possible and necessary for the patient, the sponsor held deliberations with the investigator and accepted the continuation of darinaparsin at the discretion of the sponsor.

30) If the patient wishes to continue receiving darinaparsin, and the investigator considers that the continuation of darinaparsin is possible and necessary for the patient, the treatment with darinaparsin was continued.

31) Of the 2 patients who did not receive darinaparsin, 1 patient was found not to meet the inclusion criteria after enrollment, and the other patient died before the start of treatment with darinaparsin.

darinaparsin (57 subjects) were included in the full analysis set (FAS[32]), which was used for efficacy analyses (36 Japanese subjects were included).

Table 19 shows the results for the primary endpoint, which is overall response rate[33] by central review according to the Revised Response Criteria for Malignant Lymphoma (Revised RC) (*J Clin Oncol.* 2007;25:579-86), in the overall study population and Japanese subpopulation.

Table 19. Best overall response and overall response rate (central review, FAS)

Best overall response	n (%)	
	Overall study population N = 57	Japanese subpopulation N = 36
CR	5 (8.8)	3 (8.3)
PR	6 (10.5)	5 (13.9)
SD	15 (26.3)	10 (27.8)
PD	31 (54.4)	18 (50.0)
Overall response (CR or PR)	11	8
(Overall response rate [90% CI] (%)*)	(19.3 [11.2, 29.9])	(22.2 [11.6, 36.5])

*, Exact interval based on the Clopper-Pearson method

The overall response rate [90% CI] (%) by the central review was 18.9% [9.2, 32.6] (7 of 37) of patients with relapsed[34] PTCL, and 25.0% [9.0, 48.4] (4 of 16[35]) of patients with refractory[36] PTCL.

During the treatment period of darinaparsin and within 21 days of the end of treatment, 6 of 65 subjects (9.2%) died. Two subjects died of disease progression. Other causes of death were haemophagocytic lymphohistiocytosis, tumour lysis syndrome, hypothermia, and multiple organ dysfunction syndrome in 1 subject each. A causal relationship to darinaparsin could not be ruled out for hypothermia in 1 subject[37] (1 Japanese patient died of disease progression).

32) Of the 65 subjects who received darinaparsin, a total of 8 subjects were excluded: 2 subjects who were diagnosed as having histological subtypes other than PTCL by the central review; 5 subjects who were not assessed for antitumor response after the start of treatment with darinaparsin; 1 subject who was assessed as ineligible based on the inclusion criterion of a life expectancy of at least 3 months (this patient, whose condition had seriously deteriorated from the time of screening, was assessed as having PD on Day 3 of Cycle 1, after receiving 2 doses of darinaparsin, and died on Day 10 due to disease progression).

33) Taking into account the overall response rates for existing therapies used to treat relapsed or refractory PTCL (e.g., *J Clin Oncol.* 2014;32:1157-63), a threshold response rate of 10% was selected.

34) Patients who were assessed as having CR, complete response unconfirmed (CRu), or PR in response to most recent therapies.

35) The response to the most recent therapy was not evaluable or unclear in 4 patients; none of these patients were assessed as achieving response.

36) Patients who were assessed as having SD or PD in response to the most recent therapy.

37) This patient, a man aged 6[redacted] years with peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), developed stupor accompanied by fluctuating orientation on Day 4 in Cycle 1. The patient developed septic shock on Day 5, and vasopressor treatment was started. Candida was detected in the blood culture of the sample from the implantable subcutaneous infusion port. On Day 7, the implantable subcutaneous infusion port was removed. Treatment with micafungin sodium was started, and the dose of vasopressor was reduced. Hypothermia had continued from before the start of treatment with darinaparsin with a body temperature of 35°C to 36.5°C. On Day 15, the patient had bradycardia and cardiac arrest. The patient died of hypothermia and cardiac arrest, as determined by the investigator. A causal relationship between darinaparsin and septic shock could not be ruled out, and hypothermia was determined to be related to darinaparsin.

7.1.3 Foreign clinical study

7.1.3.1 Foreign phase I study (CTD 5.3.3.2.2, Study 03 [October 2012 to January 2014])

An open-label, uncontrolled study was conducted at 1 foreign study center to investigate various aspects of darinaparsin including safety and PK in patients with relapsed or refractory PTCL (target sample size, 6 subjects in total; 3 subjects each in Cohorts 1 and 2).

The dosage regimens were as follows: in Cohort 1, darinaparsin 300 mg/m^2 on Days 1 to 5 in 28-day cycles, and in Cohort 2, darinaparsin 300 mg/m^2 on Days 1 to 5 in 21-day cycles. Darinaparsin was administered as an intravenous infusion over approximately 1 hour. Subjects were to continue treatment for up to 4 cycles unless there was disease progression or the treatment discontinuation criteria were met.[29)]

All 6 subjects enrolled in the study (3 subjects each in Cohorts 1 and 2) received darinaparsin. These subjects were included in the safety analysis set and evaluated for DLT.

In the first cycle, which was defined as the DLT assessment period (for 28 days after the start of darinaparsin treatment in Cohort 1, and for 21 days after the start of darinaparsin treatment in Cohort 2), no DLTs were observed.

No deaths were reported during the treatment period and within 28 days of the end of treatment with darinaparsin.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase I study (CTD 5.3.3.2.3, Study SGL1001 [May 2005 to May 2006])

An open-label, uncontrolled study was conducted at 1 foreign study center to investigate the safety and PK of darinaparsin in patients with relapsed or refractory hematopoietic malignancies (target sample size, 20 subjects maximum).

All 11 subjects enrolled in the study (4 subjects in the 78 mg/m^2 cohort, 3 subjects in the 109 mg/m^2 cohort, 3 subjects in the 153 mg/m^2 cohort, and 1 subject in the 214 mg/m^2 cohort) received darinaparsin and were included in the safety analysis set.

No deaths were reported during the treatment period and within 30 days of the end of treatment with darinaparsin.

7.2.1.2 Foreign phase I study (CTD 5.3.3.2.4, Study SGL1002 [July 2005 to July 2007])

An open-label, uncontrolled study was conducted at 1 foreign study center to investigate the safety and PK of darinaparsin in patients with advanced solid tumors (target sample size, 40 subjects).

Of 41 subjects enrolled in the study, 40 subjects[38] (4 subjects in the 78 mg/m^2 cohort, 3 subjects in the 109 mg/m^2 cohort, 5 subjects in the 153 mg/m^2 cohort, 3 subjects in the 214 mg/m^2 cohort, 6 subjects in the 300 mg/m^2 cohort, 11 subjects in the 420 mg/m^2 cohort, 4 subjects in the 500 mg/m^2 cohort, and 4 subjects in the 588 mg/m^2 cohort) received darinaparsin, and were included in the safety analysis set.

During the treatment period or within 30 days of the end of treatment with darinaparsin, 1 of 11 subjects (9.1%, pneumonia) in the 420 mg/m^2 cohort and 1 of 4 subjects (25.0%, systemic inflammatory response syndrome) in the 500 mg/m^2 cohort died. A causal relationship to darinaparsin was denied for both events.

7.2.1.3 Foreign phase I/II study (CTD 5.3.3.2.5, Study SGL2001 [January 2006 to August 2007])

An open-label, uncontrolled study was conducted at 8 foreign study centers to investigate safety and other aspects of darinaparsin in patients with refractory MM (target sample size, 48 subjects in total; 21 subjects in the phase I part and 27 subjects in the phase II part).

Of 32 subjects enrolled in the study, 31 subjects[39] (Phase I part: 3 subjects in the 109 mg/m^2 cohort, 3 subjects in the 153 mg/m^2 cohort, 4 subjects in the 214 mg/m^2 cohort, 3 subjects in the 300 mg/m^2 cohort, and 4 subjects in the 420 mg/m^2 cohort; Phase II part: 14 subjects in the 300 mg/m^2 cohort) received darinaparsin and were included in the safety analysis set.

During the treatment period or within 30 days of the end of treatment with darinaparsin, 1 of 4 subjects (25.0%; injury/subdural haematoma) in the 214 mg/m^2 cohort of Phase I part and 1 of 14 subjects (7.1%; infection) in the 300 mg/m^2 cohort in Phase II part died. A causal relationship to darinaparsin was denied for both events.

7.2.1.4 Foreign phase II study (CTD 5.3.5.4.1, Study SGL2001b [February 2007 to March 2008])

An open-label, uncontrolled study was conducted at 10 foreign study centers to investigate safety and other aspects of darinaparsin in patients with refractory MM (target sample size, 40 subjects in total; 26 subjects in Stage 1 and 14 subjects in Stage 2).

All 17 subjects[40] enrolled in the study received darinaparsin and were included in the safety analysis set.

Six of 17 subjects (35.3%) died during the treatment period or within 30 days of the end of treatment with darinaparsin. Four subjects died of disease progression, and other causes of death were neutropenic

[38] One subject did not have malignancy findings in the biopsy of mass lesion, and darinaparsin was not administered to this subject.

[39] One subject was found to be not meeting the inclusion criteria when anomalies were detected in the electrocardiogram taken prior to infusion of the first dose of darinaparsin, and therefore, darinaparsin was not administered to this subject.

[40] This study consisted of 2 stages. When SD or higher efficacy was achieved in ≥1 subject in Stage 1, the study was to advance to Stage 2. However, because the conditions to advance to Stage 2 were not met, the study ended at the completion of Stage 1.

sepsis and acute kidney injury in 1 subject each. A causal relationship to darinaparsin was denied for all these events.

7.2.1.5 Foreign phase II study (CTD 5.3.5.4.2, Study SGL2003 [December 2006 to June 2009])

An open-label, uncontrolled study was conducted at 11 foreign study centers to investigate safety and other aspects of darinaparsin in patients with refractory hematopoietic malignancies (target sample size, 70 subjects).

All 50 subjects enrolled in the study received darinaparsin and were included in the safety analysis set.

During the treatment period or within 28 days of the end of treatment with darinaparsin, 23 of 50 subjects (46.0%) died. Twelve subjects died of disease progression. Other causes of death were organ failure, hypotension/haemothorax, asthenia, respiratory failure/disease progression, pseudomonal sepsis/lobar pneumonia, dyspnoea/abdominal distension/hypotension/escherichia sepsis, cerebral haemorrhage, leukocytosis/thrombocytopenia/coagulation test abnormal, haemoperitoneum, respiratory failure, and anaemia/decreased appetite/disease progression in 1 subject each. A causal relationship to darinaparsin was denied for all these events.

7.2.1.6 Foreign phase II study (CTD 5.3.5.4.3, Study SGL2005 [May 2007 to September 2008])

An open-label, uncontrolled study was conducted at 10 foreign study centers to investigate safety and other aspects of darinaparsin in patients with advanced hepatocellular carcinoma (target sample size, approximately 40 subjects in total; 14 subjects in Stage 1 and up to 37 subjects in Stage 2 [including subjects of Stage 1)).

All 15 subjects[41)] enrolled in the study received darinaparsin and were included in the safety analysis set.

During the treatment period or within 30 days of the end of treatment with darinaparsin, 3 of 15 subjects (20.0%) died. Two subjects died of disease progression, and 1 subject died of gastrointestinal haemorrhage. A causal relationship to darinaparsin was denied for these events.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

Of the evaluation data submitted, PMDA concluded that the global phase II study (Study 02) in patients with relapsed or refractory PTCL was the pivotal study in evaluating the efficacy and safety of darinaparsin. Therefore, PMDA decided to conduct an efficacy and safety review mainly focusing on Study 02.

41) This study consisted of 2 stages. When response was achieved after administration of darinaparsin in Stage 1, addition of subjects was planned up to 37 subjects. However, because response was not observed, the study ended at the completion of Stage 1.

PMDA decided to assess the efficacy in Japanese patients based on the data from Study 02 and other data in a systematic manner taking into account guidelines and principles including the following: "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007); "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012); and "General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

7.R.2 Efficacy

PMDA concluded that darinaparsin has a certain level of efficacy in the treatment of patients with relapsed or refractory PTCL, based on the following discussions.

7.R.2.1 Efficacy endpoints and evaluation results

In Study 02, the lower limit of 90% confidence interval of the overall response rate by central review according to the Revised RC, which is the primary endpoint for this study, exceeded the prespecified threshold response rate of 10% [see Section 7.1.2.1].[42)] The overall response rate for the efficacy analysis set[43)] (4 subjects) of Cohort 3 in Study 01 was 50% (2 of 4 subjects, PR in 2 subjects).

Figure 1 shows the maximum change from baseline in the overall tumor size (the sum of the product of diameters) of nodal/extranodal target lesions in patients with measurable lesions at baseline in Study 02. The median duration of response assessed by the investigator,[44)] the secondary endpoint, and its 90% confidence interval was 5.2 months [2.70, 12.60].[45)]

42) Of the 8 subjects who were excluded from the FAS, 2 subjects were diagnosed as having histological subtypes other than PTCL by the central review. When the remaining 6 subjects were included in the efficacy analysis set and handled as non-evaluable (non-responders), the overall response rate by central review with its 90% confidence interval was 17.5% [10.1, 27.2] (11 of 63 subjects).

43) Patients who had received ≥2 cycles of darinaparsin and received ≥1 antitumor response assessment.

44) Because assessment by the central review was performed for up to 6 cycles, the duration of response was evaluated by the investigator.

45) The duration of response ranged 0 to 40.5 months.

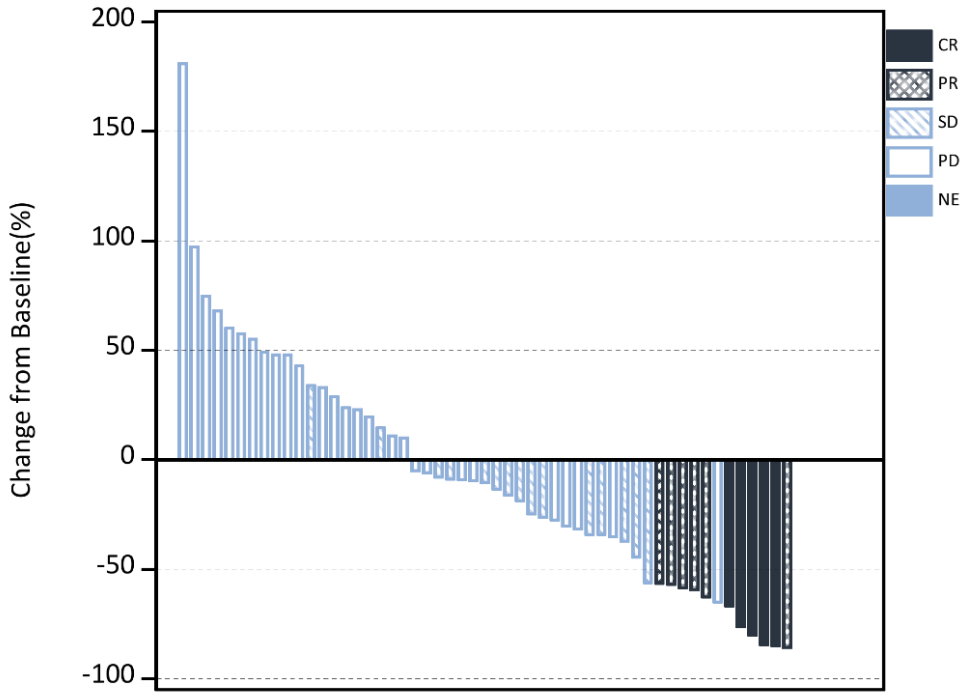

Figure 1. Maximum change from baseline in the overall tumor size (the sum of the product of diameters) of nodal/extranodal target lesions (Revised RC, Study 02, FAS, central review)

In Study 02, the overall response rate by central review according to the Revised RC and its 90% confidence interval in the Japanese subpopulation was 22.2% [11.6, 36.5], which did not differ markedly from the result for the overall population [see Section 7.1.2.1].

The applicant's explanation about the overall response rate according to Revised RC, the primary endpoint for Study 02:
The prognosis of patients with relapsed or refractory PTCL is poor, and no standard of care that demonstrated extension of overall survival (OS) has been established. In view of these and other factors, achieving overall response in this patient population is considered clinically meaningful.

PMDA's discussion:
The applicant's explanation about the efficacy endpoints is understandable, and PMDA concluded that the above results and other data demonstrated a certain level of efficacy of darinaparsin in the treatment of patients with relapsed or refractory PTCL.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events and other findings reported in clinical studies"]

On the basis of the discussions in the following sections, PMDA concluded that adverse events of special interest when using darinaparsin are myelosuppression, infection, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, and QT interval prolonged, and that patients should be carefully monitored for these adverse events when using darinaparsin.

Although the use of darinaparsin requires caution particularly for the adverse events listed above, PMDA concluded that patients should be able to tolerate darinaparsin provided that appropriate measures such as monitoring and control of adverse events, dose interruption/reduction, and treatment discontinuation are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies. However, given that the number of Japanese patients treated with darinaparsin is extremely limited, PMDA concluded that the applicant should collect more safety information in the post-marketing setting [see Section 7.R.6].

7.R.3.1 Safety profiles of darinaparsin

The applicant's explanation about the safety profiles of darinaparsin:

Table 20 summarizes the safety data from Study 02.

Table 20. Summary of safety data (Study 02)

	n (%)		
	Overall study population N = 65	Japanese subpopulation N = 37	Non-Japanese subpopulation N = 28
All adverse events	64 (98.5)	37 (100)	27 (96.4)
those for which a causal relationship to darinaparsin could not be ruled out	45 (69.2)	27 (73.0)	18 (64.3)
Grade ≥3 adverse events	41 (63.1)	26 (70.3)	15 (53.6)
Adverse events leading to death	6 (9.2)	1 (2.7)	5 (17.9)
Serious adverse events	30 (46.2)	18 (48.6)	12 (42.9)
Adverse events leading to treatment discontinuation	10 (15.4)	7 (18.9)	3 (10.7)
Adverse events leading to dose interruption	14 (21.5)	9 (24.3)	5 (17.9)
Adverse events leading to dose reduction	4 (6.2)	4 (10.8)	0

Table 21 shows adverse events of any grade occurring in ≥15% of subjects in either the Japanese or non-Japanese subpopulation in Study 02.

Table 21. Adverse events occurring in ≥15% of subjects in either the Japanese or non-Japanese subpopulation (Study 02)

SOC PT (MedDRA/J ver.23.0)	n (%)					
	Overall study population N = 65		Japanese subpopulation N = 37		Non-Japanese subpopulation N = 28	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	64 (98.5)	41 (63.1)	37 (100)	26 (70.3)	27 (96.4)	15 (53.6)
Blood and lymphatic system disorders						
Anaemia	16 (24.6)	10 (15.4)	12 (32.4)	8 (21.6)	4 (14.3)	2 (7.1)
Metabolism and nutrition disorders						
Decreased appetite	13 (20.0)	1 (1.5)	7 (18.9)	0	6 (21.4)	1 (3.6)
Gastrointestinal disorders						
Constipation	12 (18.5)	0	6 (16.2)	0	6 (21.4)	0
Skin and subcutaneous tissue disorders						
Rash	10 (15.4)	2 (3.1)	6 (16.2)	1 (2.7)	4 (14.3)	1 (3.6)
General disorders and administration site conditions						
Pyrexia	27 (41.5)	2 (3.1)	17 (45.9)	2 (5.4)	10 (35.7)	0
Malaise	9 (13.8)	0	9 (24.3)	0	0	0
Disease progression	8 (12.3)	6 (9.2)	7 (18.9)	5 (13.5)	1 (3.6)	1 (3.6)
Fatigue	7 (10.8)	2 (3.1)	0	0	7 (25.0)	2 (7.1)
Investigations						
AST increased	12 (18.5)	2 (3.1)	9 (24.3)	1 (2.7)	3 (10.7)	1 (3.6)
Platelet count decreased	11 (16.9)	6 (9.2)	6 (16.2)	3 (8.1)	5 (17.9)	3 (10.7)
ALT increased	10 (15.4)	0	6 (16.2)	0	4 (14.3)	0

In Study 02, adverse events that led to death were disease progression (2 subjects, 3.1%); haemophagocytic lymphohistiocytosis, tumour lysis syndrome, hypothermia, and multiple organ dysfunction syndrome (1 subject each, 1.5%). Among these, a causal relationship to darinaparsin could not be ruled out for hypothermia (1 subject). Serious adverse events were disease progression (7 subjects, 10.8%); pyrexia (5 subjects, 7.7%); abdominal pain (2 subjects, 3.1%); bacteraemia, epiglottitis, herpes zoster, pharyngitis, pneumonia, septic shock, sinusitis, urinary tract infection, *Enterobacter* infection, respiratory tract infection, device related sepsis, tumour associated fever, disseminated intravascular coagulation, lymphadenitis, anaphylactic shock, haemophagocytic lymphohistiocytosis, dehydration, tumour lysis syndrome, decreased appetite, confusional state, cerebral infarction, vertigo, peripheral ischaemia, deep vein thrombosis, pneumonia aspiration, pulmonary embolism, tracheal stenosis, dysphagia, biliary fistula, acute kidney injury, fatigue, hypothermia, multiple organ dysfunction syndrome, and spinal compression fracture (1 subject each, 1.5%). A causal relationship to darinaparsin could not be ruled out for pyrexia (2 subjects); abdominal pain, herpes zoster, pneumonia, septic shock, sinusitis, *Enterobacter* infection, dehydration, confusional state, cerebral infarction, vertigo, fatigue, and hypothermia (1 subject each). No adverse events led to treatment discontinuation, dose interruption, or dose reduction with an incidence of ≥5%.

In Study 02, adverse events of any grade with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation by ≥10% were pyrexia (17 subjects, 45.9% and 10 subjects, 35.7% in the Japanese and non-Japanese subpopulations, respectively; the same applies hereinafter), anaemia (12 subjects, 32.4%; 4 subjects, 14.3%), malaise (9 subjects, 24.3%; 0 subjects), AST increased (9 subjects, 24.3%; 3 subjects, 10.7%), disease progression (7 subjects, 18.9%; 1 subject, 3.6%), lymphopenia (4 subjects, 10.8%; 0 subjects), neutropenia (4 subjects, 10.8%; 0 subjects), and white

blood cell count decreased (4 subjects, 10.8%; 0 subjects). Likewise, Grade ≥3 adverse events with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation by ≥10% were anaemia (8 subjects, 21.6%; 2 subjects, 7.1%) and lymphopenia (4 subjects, 10.8%; 0 subjects). Serious adverse events with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation by ≥5% were disease progression (6 subjects, 16.2%; 1 subject, 3.6%) and pyrexia (4 subjects, 10.8%; 1 subject, 3.6%). No adverse events led to death with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation by ≥5%, or treatment discontinuation, dose interruption, or dose reduction with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation by ≥10%.

PMDA's discussion:
When using darinaparsin, healthcare professionals should pay particular attention to serious adverse events, Grade ≥3 adverse events, and adverse events with an incidence higher in the Japanese subpopulation than in the non-Japanese subpopulation that occurred in Study 02. PMDA concluded that information on the incidence of these adverse events should be provided to healthcare professionals in an appropriate manner using the package insert and other materials.

In the following sections, PMDA decided to analyze data, based mainly on safety-related results in Study 02, focusing on adverse events including serious adverse events and Grade ≥3 adverse events for which a causal relationship could not be ruled out, and also review data on the incidence of adverse events in Studies 01 and 03 including serious adverse events and Grade ≥3 adverse events. In addition, because of the extremely limited number of patients treated with darinaparsin, data from other clinical studies were also reviewed for adverse events occurring at lower frequencies.

7.R.3.2 Haematotoxicity

The applicant's explanation about the incidence of haematotoxicity by darinaparsin:
Haematotoxicity-related adverse events classified as preferred terms (PTs) under the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) "blood and lymphatic system disorders" and MedDRA high level group term (HLGT) "haematology investigations (incl blood groups)" were analyzed.

Table 22 shows the incidence of haematotoxicity in Study 02.

Table 22. Incidence of haematotoxicity occurring in ≥2 subjects (Study 02)

PT (MedDRA/J ver.23.0)	n (%) N = 65	
	All Grades	Grade ≥3
Haematotoxicity	27 (41.5)	22 (33.8)
Anaemia	16 (24.6)	10 (15.4)
Platelet count decreased	11 (16.9)	6 (9.2)
Neutrophil count decreased	7 (10.8)	6 (9.2)
Lymphopenia	4 (6.2)	4 (6.2)
Neutropenia	4 (6.2)	2 (3.1)
White blood cell count decreased	4 (6.2)	3 (4.6)
Leukopenia	3 (4.6)	3 (4.6)
Thrombocytopenia	3 (4.6)	3 (4.6)
Lymphocyte count decreased	3 (4.6)	2 (3.1)
Disseminated intravascular coagulation	2 (3.1)	1 (1.5)
APTT prolonged	2 (3.1)	1 (1.5)

In Study 02, serious haematotoxicity events occurred in 2 subjects (3.1%, disseminated intravascular coagulation and lymphadenitis in 1 subject each), and a causal relationship to darinaparsin was denied for both events. Haematotoxicity events led to treatment discontinuation of darinaparsin in 1 subject (1.5%), dose interruption of darinaparsin in 1 subject (1.5%), and dose reduction of darinaparsin in 1 subject (1.5%). No haematotoxicity events resulted in death.

In Study 01, Grade ≥3 haematotoxicity events occurred in 1 subject (33.3%; anaemia) in the 200 mg/m^2 cohort, 3 subjects (42.9%; white blood cell count decreased in 3 subjects; lymphocyte count decreased and neutrophil count decreased in 2 subjects each; anaemia, lymphopenia, and neutropenia in 1 subject each; some subjects experienced ≥2 events) in the 300 mg/m^2 cohort (4-week cycles), 3 subjects (42.9%; neutrophil count decreased and platelet count decreased in 2 subjects each; anaemia, febrile neutropenia, lymphopenia, activated partial thromboplastin time [APTT] prolonged, lymphocyte count decreased, and white blood cell count decreased in 1 subject each; some subjects experienced ≥2 events) in the 300 mg/m^2 cohort (3-week cycles). No haematotoxicity events led to death, and there were no serious haematotoxicity events.

In Study 03, Grade ≥3 haematotoxicity events occurred in 1 subject (33.3%; thrombocytopenia) in the 300 mg/m^2 cohort (3-week cycles). No haematotoxicity events led to death, and there were no serious haematotoxicity events.

PMDA's discussion:

Given that Grade ≥3 myelosuppression occurred commonly in subjects receiving darinaparsin in Japanese and foreign clinical studies, patients should be monitored for the occurrence of myelosuppression during treatment with darinaparsin. Therefore, PMDA concluded that the applicant should provide information on the incidence of myelosuppression in the clinical studies to healthcare professionals, and provide cautionary statements in the package insert and other information materials in an appropriate manner to ensure that hematology testing is performed on a regular basis during

treatment with darinaparsin, and that dose interruption, dose reduction, treatment discontinuation, or other appropriate measures should be taken to manage any abnormal results.

7.R.3.3 Infections

The applicant's explanation about the incidence of infections associated with darinaparsin:
Infection-related adverse events classified as PTs under the MedDRA SOC "Infections and infestations" were analyzed.

Table 23 shows the incidence of infections in Study 02.

Table 23. Incidence of infections occurring in ≥2 subjects (Study 02)

PT (MedDRA/J ver.23.0)	n (%) N = 65	
	All Grades	Grade ≥3
Infections	27 (41.5)	10 (15.4)
Nasopharyngitis	6 (9.2)	0
Upper respiratory tract infection	6 (9.2)	0
Pharyngitis	4 (6.2)	2 (3.1)
Oral candidiasis	3 (4.6)	0
Tonsillitis	3 (4.6)	0
Conjunctivitis	2 (3.1)	0
Gingivitis	2 (3.1)	1 (1.5)
Sinusitis	2 (3.1)	2 (3.1)

In Study 02, serious infections occurred in 8 subjects (12.3%; bacteraemia, epiglottitis, herpes zoster, pharyngitis, pneumonia, septic shock, sinusitis, urinary tract infection, *Enterobacter* infection, respiratory tract infection, and device related sepsis in 1 subject each; some subjects experienced ≥2 events). A causal relationship to darinaparsin could not be ruled out for herpes zoster, pneumonia, septic shock, sinusitis, and *Enterobacter* infection. Infections led to dose interruption of darinaparsin in 7 subjects (10.8%). No infections led to death, treatment discontinuation or reduction of darinaparsin.

In Study 01, Grade ≥3 infections occurred in 1 subject (14.3%; bacteraemia) in the 300 mg/m^2 cohort (3-week cycles). No infections led to death, and there were no serious infections.

In Study 03, Grade ≥3 infections occurred in 1 subject (33.3%; pneumonia) in the 300 mg/m^2 cohort (4-week cycles) and 1 subject (33.3%; sepsis) in the 300 mg/m^2 cohort (3-week cycles). Serious infections occurred in 1 subject (33.3%; pneumonia) in the 300 mg/m^2 cohort (4-week cycles) and 1 subject (33.3%; sepsis) in the 300 mg/m^2 cohort (3-week cycles). A causal relationship to darinaparsin was denied for both events. No infections led to death.

PMDA asked the applicant to explain (1) the status of screening/monitoring and (2) incidence of infection and status of prophylaxis for opportunistic infections (including reactivation of virus) and hepatitis B virus (HBV) infection.

The applicant's explanation:

Concerning (1), patients who tested positive for hepatitis B surface antigen, patients who tested positive for anti-hepatitis B surface antibodies or positive for anti-hepatitis B core antibodies, and positive for HBV-DNA at screening were excluded.

Concerning (2), although there were no specifications on prophylaxis for opportunistic infections and HBV infection, prophylaxis was given at the discretion of the investigator as follows:

- No prophylaxis was given against infections caused by cytomegalovirus (CMV),[46] which occurred in 1 of 65 subjects (1.5%).
- No prophylaxis was given against infections caused by *Mycobacterium tuberculosis* bacteria.[47] There were no reports of infections caused by *Mycobacterium tuberculosis* bacteria.
- Prophylaxis against infections caused by *Pneumocystis jirovecii*[48] was given to 38 of 65 subjects (58.5%). There were no reports of infections caused by *Pneumocystis jirovecii* regardless of prophylaxis.
- Prophylaxis against infections caused by varicella zoster virus (VZV)[49] was given to 14 of 65 subjects (21.5%). Infection caused by VZV occurred in 1 of 51 subjects (2.0%). This subject did not receive prophylaxis.
- Prophylaxis against infections caused by HBV[50] was given to 1 of 65 subjects (1.5%). There were no reports of infections caused by HBV regardless of prophylaxis.

PMDA's discussion:

Even though the number of patients evaluated in the Japanese and foreign clinical studies is limited, serious infections (including opportunistic infections) for which a causal relationship to darinaparsin could not be ruled out were reported in several patients. In consideration of this and other factors, patients should be closely monitored for infections when receiving treatment with darinaparsin. PMDA concluded that the applicant should include information on the incidence of infections including opportunistic infections in the clinical studies using the package insert and other materials in an appropriate manner to caution healthcare professionals, and that it is appropriate to provide the details of prophylaxis and other precautionary measures against infections implemented in Study 02 to healthcare professionals using information materials.

7.R.3.4 Psychiatric disorders

The applicant's explanation about the incidence of psychiatric disorders associated with darinaparsin:

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46) Events classified as MedDRA PTs under high level term (HLT) "cytomegaloviral infections" and PT "cytomegalovirus test positive" were analyzed.

47) Events classified as MedDRA PTs under HLT "tuberculous infections" and PT "BCG related cystitis" were analyzed.

48) Events classified as MedDRA PTs under HLT "pneumocystis infections" and MedDRA PT "pneumocystis test positive" were analyzed.

49) MedDRA PTs containing "varicella" (however, "varicella virus test negative" and "varicella post vaccine" were excluded) and MedDRA PTs containing "herpes zoster" were analyzed.

50) MedDRA PTs "chronic hepatitis B," "hepatitis B," "congenital hepatitis B," "hepatitis B reactivation," "acute hepatitis B," "hepatitis virus-associated nephropathy," "HBV-DNA polymerase increased," and "perinatal HBV infection" were analyzed.

Psychiatric disorder-related adverse events classified as MedDRA PTs under SOC "psychiatric disorders" were analyzed.

Table 24 shows the incidence of psychiatric disorders in Study 02.

Table 24. Incidence of psychiatric disorders (Study 02)

PT (MedDRA/J ver.23.0)	n (%) N = 65	
	All Grades	Grade ≥3
Psychiatric disorders	14 (21.5)	4 (6.2)
Delirium	8 (12.3)	2 (3.1)
Insomnia	4 (6.2)	0
Confusional state	3 (4.6)	1 (1.5)
Anxiety	2 (3.1)	0
Hallucination	2 (3.1)	1 (1.5)
Disorientation	1 (1.5)	1 (1.5)
Delirium febrile	1 (1.5)	0

In Study 02, a serious psychiatric disorder event occurred in 1 subject (1.5%; confusional state), and a causal relationship to darinaparsin could not be ruled out. Psychiatric disorders led to dose interruption in 3 subjects (4.6%) and dose reduction in 1 subject (1.5%). No psychiatric disorders led to death or treatment discontinuation of darinaparsin.

In Study 01, no psychiatric disorders led to death. There were no Grade ≥3 psychiatric disorders or serious psychiatric disorders.

In Study 03, serious psychiatric disorder occurred in 1 subject (33.3%; hallucination) in the 300 mg/m^2 cohort (3-week cycles), and a causal relationship to darinaparsin could not be ruled out for this event. There were no Grade ≥3 psychiatric disorders. No psychiatric disorders led to death.

The incidences of psychiatric disorders in foreign clinical studies (Studies SGL1001, SGL1002, SGL2001, and SGL2003) were as follows[51)]:

- In Study SGL2001, Grade ≥3 psychiatric disorders occurred in 3 subjects (17.6%; confusional state in 3 subjects) in the 300 mg/m^2 cohort. Serious psychiatric disorders occurred in 2 subjects (11.8%; confusional state in 2 subjects) in the 300 mg/m^2 cohort. A causal relationship to darinaparsin could not be ruled out for any of the events. No psychiatric disorders led to death.
- In Study SGL2003, Grade ≥3 psychiatric disorders occurred in 2 subjects (4.0%; agitation and confusional state in 1 subject each). A serious psychiatric disorder occurred in 1 subject (2.0%; confusional state), and a causal relationship to darinaparsin was denied. No psychiatric disorders led to death.
- In Studies SGL1001 and SGL1002, no psychiatric disorders led to death. There were no Grade ≥3 psychiatric disorders or serious psychiatric disorders.

51) Adverse events that occurred at or below the proposed dosage were evaluated. Data from Studies SGL2001b and SGL2005, in which darinaparsin 420 mg/m^2 was administered, were not included in the evaluation.

All of the above-mentioned events of psychiatric disorders for which a causal relationship to darinaparsin could not be ruled out resolved except for the following events in Study 02: confusional state (Grade 2), anxiety (Grade 2), and delirium (Grade 3). These 3 subjects with unresolved psychiatric disorders were able to continue receiving darinaparsin after treatment with symptomatic therapies or other measures.

PMDA's discussion:
When using darinaparsin, the patient should be closely monitored for development of psychiatric disorders (e.g., delirium and confusion), given that serious psychiatric disorders, for which a causal relationship to darinaparsin could not be ruled out, were reported in Japanese and foreign clinical studies, and Grade ≥3 psychiatric disorders were reported in several patients. Therefore, PMDA concluded that the applicant should provide information to healthcare professionals on the incidence of psychiatric disorders in the clinical studies and include cautionary statements in the package insert and other materials in an appropriate manner so that healthcare professionals will pay particular attention to changes in the patient's mental state during treatment with darinaparsin and if psychiatric disorders such as delirium and confusion are observed, dose interruption, dose reduction, treatment discontinuation, or other actions should be taken.

7.R.3.5 Nervous system disorders

The applicant's explanation about the incidence of nervous system disorders associated with darinaparsin:
Nervous system disorder-related adverse events classified as MedDRA PTs under SOC "nervous system disorders" were analyzed.

Table 25 shows the incidence of nervous system disorders in Study 02.

Table 25. Incidence of nervous system disorders (Study 02)

PT (MedDRA/J ver.23.0)	n (%) N = 65	
	All Grades	Grade ≥3
Nervous system disorders	26 (40.0)	3 (4.6)
Dizziness	5 (7.7)	0
Headache	5 (7.7)	0
Peripheral sensory neuropathy	5 (7.7)	0
Dysgeusia	4 (6.2)	0
Hypoaesthesia	3 (4.6)	0
Somnolence	3 (4.6)	0
Neuropathy peripheral	2 (3.1)	1 (1.5)
Cognitive disorder	1 (1.5)	1 (1.5)
Vertigo	1 (1.5)	1 (1.5)
Cerebral infarction	1 (1.5)	0
Syncope	1 (1.5)	0
Dementia with Lewy bodies	1 (1.5)	0
Taste disorder	1 (1.5)	0

In Study 02, serious nervous system disorders occurred in 2 subjects (3.0%; cerebral infarction and vertigo in 1 subject each), and a causal relationship to darinaparsin could not be ruled out for either of the events. Nervous system disorders led to treatment discontinuation of darinaparsin in 3 subjects (4.6%), dose interruption in 2 subjects (3.1%), and dose reduction in 1 subject (1.5%). No nervous system disorders led to death.

In Studies 01 and 03, no nervous system disorders led to death. There were no Grade ≥3 nervous system disorders or serious nervous system disorders.

The incidences of nervous system disorders in foreign clinical studies (Studies SGL1001, SGL1002, SGL2001, and SGL2003) were as follows[51)]:

- In Study SGL1001, Grade ≥3 nervous system disorders occurred in 1 subject (33.3%; seizure and somnolence; the subject experienced both events) in the 153 mg/m^2 cohort. A serious nervous system disorder occurred in 1 subject (33.3%; seizure) in the 153 mg/m^2 cohort, and a causal relationship to darinaparsin was denied. No nervous system disorders led to death.
- In Study SGL1002, Grade ≥3 nervous system disorders occurred in 1 subject (33.3%; ataxia and lacunar infarction; the subject experienced both events) in the 214 mg/m^2 cohort. Serious nervous system disorders occurred in 1 subject (25.0%; speech disorder) in the 78 mg/m^2 cohort, and 1 subject (33.3%; lacunar infarction) in the 214 mg/m^2 cohort. A causal relationship to darinaparsin was denied for both events. No nervous system disorders led to death.
- In Study SGL2001, Grade ≥3 nervous system disorders occurred in 1 subject (33.3%; headache) in the 109 mg/m^2 cohort, 1 subject (25.0%; vertigo) in the 214 mg/m^2 cohort. No nervous system disorders led to death and there were no serious nervous system disorders.
- In Study SGL2003, Grade ≥3 nervous system disorders occurred in 4 subjects (8.0%; ataxia, cerebral haemorrhage, coma, seizure, and motor dysfunction in 1 subject each; some subjects experienced >1 event). A nervous system disorder in 1 subject (2.0%; cerebral haemorrhage) led to death, and a causal relationship to darinaparsin was denied. Serious nervous system disorders occurred in 1 subject (2.0%; cerebral haemorrhage and coma; the subject experienced both events), and a causal relationship to darinaparsin was denied for both events.

PMDA's discussion:

When using darinaparsin, healthcare professionals should pay attention to central nervous system disorders based on factors including the following: (1) in Japanese and foreign clinical studies, there have been reports of serious central nervous system disorders for which a causal relationship to darinaparsin could not be ruled out; (2) Grade ≥3 central nervous system disorders have been reported in several subjects; and (3) effects on the central nervous system were observed in the non-clinical toxicity studies of darinaparsin [see Section 5.R.1]. Therefore, PMDA concluded that the applicant should provide information on the incidence of central nervous system disorders in the clinical studies to healthcare professionals, and provide cautionary statements in the package insert and other information materials in an appropriate manner to ensure that, the patient's condition is closely

monitored during the use of darinaparsin and that dose interruption, dose reduction, treatment discontinuation, or other appropriate measures should be taken in the event of any abnormal condition. Although the incidence of Grade ≥3 or serious peripheral nervous system disorders for which a causal relationship to darinaparsin could not be ruled out is relatively low, PMDA also concluded that the applicant should continue collecting post-marketing data on peripheral nervous system disorders because peripheral nervous system disorders have been reported in patients treated with arsenic trioxide, an arsenic compound.

7.R.3.6 Cardiac disorders

The applicant's explanation about the incidence of cardiac disorders associated with darinaparsin:
Cardiac disorder-related adverse events classified as MedDRA PTs under MedDRA SOC "cardiac disorders" and HLGT "cardiac and vascular investigations (excl enzyme tests)" were analyzed.

In Study 02, cardiac disorders of any grade occurred in 6 subjects (9.2%; electrocardiogram QT prolonged in 2 subjects; electrocardiogram PR prolongation, atrial fibrillation, myocarditis, and tachycardia in 1 subject each). A Grade ≥3 cardiac disorder occurred in 1 subject (1.5%; electrocardiogram QT prolonged). Cardiac disorders led to treatment discontinuation of darinaparsin in 1 subject (1.5%), dose interruption of darinaparsin in 1 subject (1.5%), and dose reduction of darinaparsin in 1 subject (1.5%). No cardiac disorders led to death. There were no serious cardiac disorders.

In Studies 01 and 03, no cardiac disorders led to death, and there were no Grade ≥3 cardiac disorders or serious cardiac disorders.

The incidence of cardiac disorders in foreign clinical studies (Studies SGL1001, SGL1002, SGL2001, and SGL2003)[51)] were as follows:

- In Study SGL1001, a Grade ≥3 cardiac disorder occurred in 1 subject (33.3%; cardiac failure congestive) in the 153 mg/m^2 cohort. No cardiac disorders led to death, and there were no serious cardiac disorders.
- In Study SGL2001, a serious cardiac disorder occurred in 1 subject (33.3%; cardiac failure congestive) in the 109 mg/m^2 cohort, and a causal relationship to darinaparsin was denied. There were no Grade ≥3 cardiac disorders. No cardiac disorders led to death.
- In Study SGL2003, Grade ≥3 cardiac disorders occurred in 4 subjects (8.0%; electrocardiogram QT prolonged in 2 subjects; cardio-respiratory arrest and sinus tachycardia in 1 subject each). One subject (2.0%) died due to cardiac disorder (cardio-respiratory arrest), and a causal relationship to darinaparsin was ruled out. Serious cardiac disorders occurred in 4 subjects (8.0%; atrial fibrillation, cardiac failure congestive, cardio-respiratory arrest, and electrocardiogram QT prolonged in 1 subject each), and a causal relationship to darinaparsin was denied for all events.
- In Study SGL1002, no cardiac disorders led to death, and there were no Grade ≥3 cardiac disorders or serious cardiac disorders.

The applicant's explanation about QT interval prolongation during treatment with darinaparsin:
In Studies 02, 01, and 03, 12-lead electrocardiography was performed on a regular basis. Table 26 shows the change in QTcF.

Table 26. Change in QTcF in patients with measured QTcF data (Studies 02, 01, and 03)

	n (%)		
	Study 02 N = 65	Study 01* N = 6	Study 03* N = 3
Maximum			
≤450 ms	44 (67.7)	4 (66.7)	2 (66.7)
>450 ms and ≤480 ms	18 (27.7)	2 (33.3)	1 (33.3)
>480 ms and ≤500 ms	2 (3.1)	0	0
>500 ms	1 (1.5)	0	0
Increase from baseline (maximum)			
<0 ms	3 (4.6)	0	1 (33.3)
≥0 ms and ≤30 ms	41 (63.1)	6 (100)	1 (33.3)
>30 ms and ≤60 ms	17 (26.2)	0	1 (33.3)
>60 ms	4 (6.2)	0	0

*: For Studies 01 and 03, only data from cohorts receiving the proposed dosage regimen (Cohort 3 of Study 01 and Cohort 2 of Study 03) were included in the analysis.

PMDA's discussion:
When using darinaparsin, healthcare professionals should pay attention to QT interval prolongation based on factors including the following: in Japanese and foreign clinical studies, some patients had high QTcF values (Table 26); and for arsenic trioxide, which is also an arsenic compound, a cautionary statement to the effect that the patient should be monitored for QT interval prolongation and other events has been included in the package insert. Therefore, PMDA concluded that the applicant should provide information on the incidence of QT interval prolongation in the clinical studies to healthcare professionals, and provide cautionary statements in the package insert and other information materials in an appropriate manner to ensure that electrocardiography or other examinations are performed as necessary, and that dose interruption, dose reduction, treatment discontinuation, or other appropriate measures should be taken in the event of any abnormal finding.

7.R.4 Clinical positioning and indication

The proposed indication of darinaparsin was "relapsed or refractory peripheral T-cell lymphoma." The following statements were specified in the Precautions Concerning Indications section:

- Diagnosis of disease suitable for darinaparsin treatment should be performed by physicians or at medical institutions with sufficient experience in diagnostic pathology.
- Whether a patient is suitable for treatment with darinaparsin should be decided only after becoming fully familiar with the details in the "Clinical Studies" section regarding histological subtypes of patients who were enrolled in the clinical studies, and gaining a thorough understanding of the efficacy and safety of darinaparsin.

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that the proposed statements for the "Indication" and "Precautions Concerning Indications" sections shown above are appropriate.

7.R.4.1 Clinical positioning of darinaparsin

In the clinical practice guidelines[52)] and representative textbooks[53)] of hematology published in Japan and other countries, no descriptions of darinaparsin for the treatment of relapsed or refractory PTCL were found.

The applicant's explanation about clinical positioning of darinaparsin for the treatment of relapsed or refractory PTCL:

Relapsed or refractory PTCL is an extremely rare disease and has a poor prognosis. No confirmatory study results have been obtained for antineoplastic agents (mogamulizumab [genetical recombination], forodesine, pralatrexate, romidepsin, brentuximab vedotin [genetical recombination], and denileukin diftitox [genetical recombination]) approved in Japan for the treatment of relapsed or refractory PTCL, and no standard of care has been established. Under such circumstances, the results from Study 02, an uncontrolled study, demonstrated the clinical benefit of darinaparsin [see Sections 7.R.2 and 7.R.3]. In consideration of the results and other factors, darinaparsin can be positioned as a treatment option for patients with relapsed or refractory PTCL.

There are no data from clinical studies that compared the clinical benefit of darinaparsin with that of authorized antineoplastic agents, which precludes establishment of clear criteria for the choice between darinaparsin and other antineoplastic agents mentioned above. It is considered that appropriate therapy will be determined by healthcare professionals after thorough consideration of the efficacy and safety of each agent, the patient's condition, and other factors.

PMDA accepted the applicant's explanation.

7.R.4.2 Patients eligible for darinaparsin and indication

The applicant's explanation about the histological subtypes of PTCL intended for the treatment with darinaparsin:

Table 27 shows the best overall response and overall response rate by central review according to the Revised RC organized by eligible histological subtypes in Study 02. Of the PTCL subtypes, an overall response was achieved in patients with PTCL-NOS and angioimmunoblastic T-cell lymphoma (AITL); therefore, darinaparsin is expected to show clinical benefit for patients with these histological subtypes.

52) *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in T-cell Lymphomas.* (NCCN Guidelines) v.1.2021 and *Practical Guidelines for Hematological Malignancies*. 2018 Revised edition [in Japanese] (edited by the Japanese Society of Hematology)

53) *Wintrobe's Clinical Hematology.* 14th Edition (Lippincott Williams & Wilkins, 2018, USA), *Williams Hematology.* 10th Edition (The McGraw-Hill Company, Inc, 2021, USA)

Table 27. Best overall response and overall response rate by histological subtype (Study 02, central review, FAS)

Histological subtype	n (%)	Best overall response				Overall response (CR or PR) (Overall response rate, %)
		CR	PR	SD	PD	
PTCL-NOS	37 (64.9)	2	4	12	19	6 (16.2)
AITL	17 (29.8)	3	2	3	9	5 (29.4)
ALK negative ALCL	3 (5.3)	0	0	0	3	0
ALK positive ALCL*	0	—	—	—	—	—

*, Although this subtype was included in the prespecified inclusion criteria, patients with the subtype were not enrolled.

In the World Health Organization (WHO) classification of 2008, PTCL is a histological subtype categorized into mature T/NK-cell neoplasms. The mature T/NK-cell neoplasms are classified into 4 categories based on the site of main lesions: nodal, extranodal, leukemic, and cutaneous. In this classification system, histological subtypes classified into the "extranodal" category[54] differ from those classified into the "nodal" category[55] in terms of disease characteristics; histological subtypes classified into the "leukemic"[56] or "cutaneous" category[57] differ from those classified into the "nodal" or "extranodal" category in terms of pathologic features, prognosis, and therapeutic strategy. Because of these and other reasons, patients with histological subtypes of the extranodal, leukemic, and cutaneous categories were excluded from the eligible population in Study 02.

However, in view of the factors below, it is considered that darinaparsin can also be used for the treatment of (1) the histological subtype that was eligible for enrollment in Study 02, but did not achieve overall response (anaplastic lymphoma kinase [ALK] negative anaplastic large cell lymphoma [ALCL]); (2) histological subtype that was not enrolled in Study 02 (ALK positive ALCL); and (3) histological subtypes classified into the "extranodal" category, which was not eligible for enrollment in Study 02, but has a similar therapeutic strategy as that of the histological subtype eligible for Study 02.

- Darinaparsin causes mitochondrial dysfunction enhancing production of intracellular ROS, which together with other factors are thought to induce apoptosis and cell cycle arrest, thereby exerting antitumor effects [see Section 3.R.1]. Because darinaparsin is not a drug targeting specific antigens or molecules, it is considered that darinaparsin will exert an antitumor effect against PTCL subtypes classified into the categories in (1), (2), and (3) above.
- Darinaparsin has been demonstrated to have a certain level of efficacy in the treatment of PTCL-NOS and AITL. In view of this and other factors, darinaparsin is expected to show efficacy also for PTCL subtypes classified into the categories in (1) and (2).

On the basis of the above, it is considered that the indication for darinaparsin can be defined as "relapsed or refractory PTCL," provided that the "Clinical Studies" section of the package insert includes descriptions regarding histological subtypes of patients intended to be enrolled in Study 02 and those of

54) Extranodal NK/T-cell lymphoma nasal type, enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, systemic EBV-positive T-cell lymphoproliferative disease of childhood, and hydroa vacciniforme-like lymphoma.
55) The histological subtypes eligible for Study 02.
56) T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, aggressive NK-cell leukemia, and adult T-cell leukemia/lymphoma.
57) e.g., mycosis fungoides, Sézary syndrome, and primary cutaneous CD30+ T-cell lymphoproliferative disorders.

patients who were actually enrolled, together with efficacy results by histological subtype, and that a statement to the effect of the following is included in the "Precautions Concerning Indications" section. In addition, diagnosis of disease suitable for darinaparsin treatment should be performed by physicians or at medical institutions with sufficient experience in diagnostic pathology; therefore, a cautionary statement to this effect should also be specified.

- For the treatment with darinaparsin, appropriate patients should be selected after becoming fully familiar with the details in the "Clinical Studies" section regarding histological subtypes of patients who were enrolled in the clinical studies, and gaining a thorough understanding of the efficacy and safety of darinaparsin.

PMDA's discussion:

On the basis of the applicant's explanation about the histological subtypes of patients intended for the treatment with darinaparsin, as well as various factors including the following, PMDA concluded that the indication for darinaparsin can be defined as "relapsed or refractory peripheral T-cell lymphoma," provided that the cautionary statements discussed above are included in the "Precautions Concerning Indications" section.

- There is no standard of care that is likely to extend OS in patients with relapsed or refractory PTCL [see Section 7.R.4.1], and a subtype-specific standard of care has not been established.
- Due to the extremely limited number of patients with relapsed or refractory PTCL, it is considered difficult to conduct a clinical study by histological subtype to evaluate the efficacy and other data of darinaparsin.
- Darinaparsin is a drug that is to be used by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.5 Dosage and administration

The proposed dosage and administration of darinaparsin was "The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over approximately 1 hour for 5 consecutive days, followed by a 16-day rest period. This cycle should be repeated. The dose may be reduced according to the patient's condition as necessary." The proposed statements for the "Precautions Concerning Dosage and Administration" section were as follows:

- The efficacy and safety of darinaparsin in combination with other antineoplastic agents have not been established.
- Dose adjustment criteria for adverse reactions

On the basis of the discussions in the following sections as well as those in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that it is appropriate to specify the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections as shown below:

Dosage and Administration

The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over 1 hour for 5 days, followed by a 16-day rest period. This 21-day treatment cycle should be repeated. The dose may be reduced, as appropriate, according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of darinaparsin in combination with other antineoplastic agents have not been established.
- If the patient develops an adverse reaction following administration of darinaparsin, the dose of darinaparsin must be interrupted, reduced, or treatment with darinaparsin must be discontinued based on the following criteria:

Criteria for dose interruption, reduction, treatment discontinuation due to adverse reactions

Adverse reaction	Action
Grade 1 or 2* psychiatric disorders such as delirium and confusion, central nervous system disorders	Interrupt doses until symptoms resolve. After symptoms resolve, treatment may be resumed at the same dose level.
Grade 3* adverse reactions (excluding nausea/vomiting, diarrhoea, and clinically irrelevant asymptomatic abnormal laboratory values)	Interrupt doses until recovery to Grade 1 or to the grade before the start of treatment. After adverse reactions resolve, treatment may be resumed at a reduced dose level of 200 mg/m^2. If adverse reactions recur after dose reduction to 200 mg/m^2, discontinue treatment.
Grade 3* nausea/vomiting, diarrhoea	If symptoms do not resolve by symptomatic therapy, interrupt doses until they resolve. After symptoms resolve, treatment may be resumed at a reduced dose level of 200 mg/m^2. If adverse reactions recur after dose reduction to 200 mg/m^2, discontinue treatment.
Grade 4* adverse reactions (excluding clinically irrelevant asymptomatic abnormal laboratory values)	Discontinue treatment.

*, The grades are in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

7.R.5.1 Dosage regimen of darinaparsin

The applicant's explanation about the dosage regimen of darinaparsin:

Data from the Japanese phase I study (Study 01) demonstrated that darinaparsin was well-tolerated up to 300 mg/m^2. In the dosage regimen of darinaparsin 300 mg/m^2 QD administered as an intravenous infusion on Days 1 to 5, followed by a 23-day rest period in 28-day cycles, the plasma arsenic concentrations on Day 15 were below the lower limit of quantitation [see Section 6.2.1.1]. Accordingly, a dosage regimen with a shorter rest period of 16 days was additionally investigated. The results demonstrated that darinaparsin was well-tolerated at the dosage regimen. In addition, there were no clear differences between the dosage regimens in terms of treatment status or the incidence of adverse events. Taking account of the results and other data, the dosage regimen for the global phase II study (Study 02) was specified as darinaparsin 300 mg/m^2 QD administered as an intravenous infusion for 5 days, followed by a 16-day rest period in 21-day cycles. The results of Study 02 demonstrated the clinical benefit of darinaparsin in the treatment of patients with relapsed or refractory PTCL, and therefore, the proposed dosage and administration were established based on the dosage regimen of Study 02.

PMDA accepted the applicant's explanation.

7.R.5.2 Dose adjustment of darinaparsin

The applicant's explanation about the rationale for the dose adjustment criteria for darinaparsin:

In Study 02, criteria for dose interruption, reduction, treatment discontinuation of darinaparsin were defined. Study 02 was conducted in accordance with the criteria, and the results demonstrated that darinaparsin was well-tolerated. On the basis of this and other factors, the dose adjustment criteria for darinaparsin[58)] were defined in the "Precautions Concerning Dosage and Administration" section equivalent to the criteria of the global phase II study (Study 02), with the following modification:

- If Grade 3 adverse events occurred in Study 02, the basic principle[59)] was to reduce the dose to 200 mg/m^2 but the protocol also allowed the patient to have an option to continue at 300 mg/m^2 without dose reduction at the discretion of the investigator, taking into account of the patient's response to supportive care for the event. However, because treatment at 300 mg/m^2 should not be continued without careful consideration, it was decided that this option is unnecessary and only dose reduction to 200 mg/m^2 was specified.

PMDA's discussion:

The applicant's explanation about the dose adjustment criteria for darinaparsin is generally acceptable. The proposed statement for the "Precautions Concerning Dosage and Administration" section to the effect that "for adverse reactions related to psychiatric disorders and nervous system disorders, dose interruption, reduction or treatment discontinuation should be considered" should be modified as shown below for reasons that include the following: (1) among "psychiatric disorders" and "nervous system disorders," adverse events that particularly require consideration of dose adjustment are psychiatric disorders (e.g., delirium and confusion) and central nervous system disorders [see Sections 7.R.3.4 and 7.R.3.5]; (2) although specific dose adjustment criteria[58)] were not specified for "psychiatric disorders" and "nervous system disorders" in Study 02, given that it is appropriate to take measures such as interrupting doses and monitoring the patient's condition when such symptoms are detected even if they are mild in severity:

- If Grade 1 or 2 psychiatric disorders such as delirium and confusion, and central nervous system disorders occur, interrupt doses until symptoms resolve, and after symptoms resolve, treatment can be resumed at the same dose level.
- If Grade ≥3 psychiatric disorders such as delirium and confusion, and central nervous system disorders occur, the dose should be adjusted in a manner equivalent to other adverse reactions.

58) A statement to the effect that "consider dose interruption, dose reduction, or treatment discontinuation regardless of the grade" was defined as the proposed dose adjustment criteria for psychiatric disorders and nervous system disorders based on those specified for Study 02.

59) For Grade 3 nausea/vomiting or diarrhoea, the protocol allowed the patient to have the option of continuing at 300 mg/m^2 at the discretion of principal investigator, with the patient's responsiveness to supportive care for the event taken into account.

7.R.5.3 Route of administration of darinaparsin

The applicant's explanation about the route of administration of darinaparsin:

At the beginning of the foreign phase I/II study (Study SGL2001), the route of administration of darinaparsin had not been specified (both peripheral and central vein were allowed); however, because abnormalities at the administration site appeared due to administration via a peripheral vein,[60] the specification on the route of administration was revised in the protocol during the study, and the revised protocol required administration via a central vein. Taking account of the change, a central vein was specified as the preferable route of administration in the Japanese and foreign clinical studies (Studies 01, 02, and 03).

Adverse events related to abnormalities at the administration site after administration of darinaparsin via a peripheral vein that occurred in Studies 01 and 02 are summarized as follows[61]:

- In Study 01, the route of administration was changed from a central vein to a peripheral vein in 3 of 17 patients (17.6%) during the study. Injection site pain (Grade 2) and vasculitis (Grade 2) occurred in 2 of the 3 patients, and the route was again changed to a central vein.
- In Study 02, darinaparsin was administered via a peripheral venous route in 4 of 65 patients (6.2%), and 2 of these patients (3.1%) developed adverse events related to abnormalities at the administration site (Grade 1 vascular pain in 2 patients), for which a causal relationship to darinaparsin could not be ruled out. The route was changed to a central vein in both patients, after which the symptom resolved. After changing to a central venous route, vascular pain did not occur, and these patients were able to continue treatment.

The above findings suggest that it is preferable to administer darinaparsin by a central venous route rather than by a peripheral venous route; therefore, a cautionary statement to this effect will be included in the package insert.

PMDA accepted the applicant's explanation.

7.R.5.4 Use of darinaparsin in combination with other antineoplastic agents

The applicant's explanation about the use of darinaparsin in combination with other antineoplastic agents in patients with relapsed or refractory PTCL:

Currently, no results have been obtained from clinical studies that evaluated the clinical benefit of darinaparsin in combination with other antineoplastic agents in patients with relapsed or refractory PTCL. Therefore, the use of darinaparsin in combination with other antineoplastic agents is not recommended in the patient population.

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60) A subject treated with darinaparsin 420 mg/m^2 developed phlebitis superficial (Grade 2, serious adverse event), for which a causal relationship to darinaparsin could not be ruled out.

61) In Study 03, darinaparsin was administered by central venous route in all patients, and there were no reports of adverse events related to abnormalities at the administration site.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about the plan for the post-marketing surveillance:
The applicant intends to conduct post-marketing surveillance covering all patients who will be receiving darinaparsin to evaluate the safety and efficacy of darinaparsin in clinical use.

Taking account of the incidence of adverse events in Study 02 and other data, the safety specification was defined as psychiatric disorders, nervous system disorders, and cardiac disorders (e.g., QT interval prolongation), as well as safety in patients with renal impairment, and use in patients with hepatic impairment.

A planned sample size of 70 was selected taking into account the incidence data from Study 02 of adverse events that are included in the safety specification of the post-marketing surveillance.

A follow-up period of 6 cycles (18 weeks) after the start of treatment with darinaparsin was selected taking into account the time to onset data from Study 02 of adverse events that are included in the safety specification of the post-marketing surveillance.

PMDA's discussion:
Because safety data on darinaparsin treatment in Japanese patients are limited, PMDA concluded that post-marketing surveillance should be conducted covering all patients who will be receiving darinaparsin for a specified period after the product launch, to collect data without delay in an unbiased manner, and the safety and efficacy data so obtained should be provided promptly to healthcare professionals.

On the basis of the discussions in Section "7.R.3 Safety," the safety specification for the post-marketing surveillance should be myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, peripheral nervous system disorders, and QT interval prolongation.

The planned sample size for the post-marketing surveillance should be reconsidered after examining the incidence and other data of the adverse events proposed for inclusion in the safety specification. On the other hand, only a limited number of patients (9 of 65 patients) received more than 6 cycles of darinaparsin in the clinical studies, and in fact some adverse events that were not reported in earlier cycles, occurred after Cycle 6. In view of the above and other reasons, the follow-up period should be longer than 6 cycles (18 weeks).

7.3 Adverse events and other findings reported in clinical studies

The following sections discuss the main adverse events, other than deaths, reported in clinical study results submitted for safety evaluation data. Deaths reported in study results are discussed in Sections "7.1 Evaluation data" and "7.2 Reference data."

7.3.1 Japanese phase I study (Study 01)

Adverse events occurred in 3 of 3 subjects (100%) in Cohort 1, 7 of 7 subjects (100%) in Cohort 2, and 7 of 7 subjects (100%) in Cohort 3. Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 3 of 3 subjects (100%) in Cohort 1, 6 of 7 subjects (85.7%) in Cohort 2, and 7 of 7 subjects (100%) in Cohort 3. Table 28 shows adverse events occurring in ≥2 subjects in any cohort.

Table 28. Adverse events occurring in ≥2 subjects in any cohort

SOC PT (MedDRA/J ver.23.1)	n (%)					
	Cohort 1 N = 3		Cohort 2 N = 7		Cohort 3 N = 7	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	7 (100)	4 (57.1)	7 (100)	4 (57.1)
Blood and lymphatic system disorders						
Anaemia	1 (33.3)	1 (33.3)	1 (14.3)	1 (14.3)	2 (28.6)	1 (14.3)
Lymphopenia	2 (66.7)	0	1 (14.3)	1 (14.3)	1 (14.3)	1 (14.3)
Metabolism and nutrition disorders						
Decreased appetite	0	0	3 (42.9)	0	0	0
Psychiatric disorders						
Insomnia	0	0	2 (28.6)	0	1 (14.3)	0
Nervous system disorders						
Somnolence	2 (66.7)	0	1 (14.3)	0	0	0
Gastrointestinal disorders						
Constipation	0	0	3 (42.9)	0	2 (28.6)	0
Nausea	0	0	2 (28.6)	0	2 (28.6)	1 (14.3)
General disorders and administration site conditions						
Malaise	2 (66.7)	0	1 (14.3)	0	1 (14.3)	0
Pyrexia	2 (66.7)	0	2 (28.6)	1 (14.3)	1 (14.3)	0
Disease progression	3 (100)	1 (33.3)	3 (42.9)	1 (14.3)	3 (42.9)	2 (28.6)
Investigations						
APTT prolonged	0	0	1 (14.3)	0	3 (42.9)	1 (14.3)
ALT increased	0	0	3 (42.9)	0	2 (28.6)	0
AST increased	0	0	2 (28.6)	0	2 (28.6)	0
C-reactive protein increased	2 (66.7)	0	2 (28.6)	0	0	0
Lymphocyte count decreased	0	0	2 (28.6)	2 (28.6)	1 (14.3)	1 (14.3)
Neutrophil count decreased	0	0	2 (28.6)	2 (28.6)	2 (28.6)	2 (28.6)
Platelet count decreased	1 (33.3)	0	2 (28.6)	0	2 (28.6)	2 (28.6)
White blood cell count decreased	1 (33.3)	0	3 (42.9)	3 (42.9)	2 (28.6)	1 (14.3)
Blood ALP increased	1 (33.3)	0	2 (28.6)	0	1 (14.3)	0

Serious adverse events occurred in 2 of 3 subjects (66.7%) in Cohort 1 and 3 of 7 subjects (42.9%) in Cohort 2, and no serious adverse events were reported in Cohort 3. The reported serious adverse events were large intestinal stenosis, pyrexia, and disease progression (1 subject each; 33.3%) in Cohort 1, diffuse large B-cell lymphoma, tonsillar hypertrophy, pyrexia, and disease progression (1 subject each; 14.3%) in Cohort 2. A causal relationship to darinaparsin could not be ruled out for pyrexia (1 subject) in Cohort 1, and diffuse large B-cell lymphoma (1 subject) in Cohort 2.

No adverse events led to treatment discontinuation of darinaparsin.

7.3.2 Global phase II study (Study 02)

Adverse events occurred in 64 of 65 subjects (98.5%). Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 45 of 65 subjects (69.2%). Table 29 shows adverse events occurring in ≥10% of subjects.

Table 29. Adverse events occurring in ≥10% of subjects

SOC PT (MedDRA/J ver.23.0)	n (%) N = 65	
	All Grades	Grade ≥3
All adverse events	64 (98.5)	41 (63.1)
Blood and lymphatic system disorders		
Anaemia	16 (24.6)	10 (15.4)
Metabolism and nutrition disorders		
Hypokalaemia	7 (10.8)	3 (4.6)
Decreased appetite	13 (20.0)	1 (1.5)
Psychiatric disorders		
Delirium	8 (12.3)	2 (3.1)
Gastrointestinal disorders		
Constipation	12 (18.5)	0
Vomiting	7 (10.8)	0
Skin and subcutaneous tissue disorders		
Pruritus	7 (10.8)	1 (1.5)
Rash	10 (15.4)	2 (3.1)
General disorders and administration site conditions		
Fatigue	7 (10.8)	2 (3.1)
Malaise	9 (13.8)	0
Pyrexia	27 (41.5)	2 (3.1)
Disease progression	8 (12.3)	6 (9.2)
Investigations		
ALT increased	10 (15.4)	0
AST increased	12 (18.5)	2 (3.1)
Neutrophil count decreased	7 (10.8)	6 (9.2)
Platelet count decreased	11 (16.9)	6 (9.2)

Serious adverse events occurred in 30 of 65 subjects (46.2%). Serious adverse events occurring in ≥2 subjects were disease progression (7 subjects; 10.8%), pyrexia (5 subjects; 7.7%), and abdominal pain (2 subjects; 3.1%). Among these events, a causal relationship to darinaparsin could not be ruled out for pyrexia (2 subjects) and abdominal pain (1 subject).

Adverse events led to treatment discontinuation of darinaparsin in 10 of 65 subjects (15.4%). None of the adverse events leading to treatment discontinuation of darinaparsin occurred in ≥2 subjects.

7.3.3 Foreign phase I study (Study 03)

Adverse events occurred in 3 of 3 subjects (100%) in Cohort 1 and 3 of 3 subjects (100%) in Cohort 2. Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 1 of 3 subjects (33.3%) in Cohort 1 and 1 of 3 subjects (33.3%) in Cohort 2. Adverse events occurring in ≥2 subjects in each cohort were decreased appetite and insomnia (2 subjects each; 66.7%) in Cohort 1, and cough and rash (2 subjects each; 66.7%) in Cohort 2.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in Cohort 1 and 3 of 3 subjects (100%) in Cohort 2. The reported serious adverse events were pneumonia (1 subject; 33.3%) in Cohort 1, and sepsis, tumour associated fever, and hallucination (1 subject each; 33.3%) in Cohort 2. Among these events, a causal relationship to darinaparsin could not be ruled out for hallucination (1 subject) in Cohort 2.

No adverse events led to treatment discontinuation of darinaparsin.

7.3.4 Foreign phase I study (Study SGL1001)

Adverse events occurred in 4 of 4 subjects (100%) in the 78 mg/m^2 cohort, 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 3 of 3 subjects (100%) in the 153 mg/m^2 cohort, and 1 of 1 subject (100%) in the 214 mg/m^2 cohort. Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 3 of 4 subjects (75.0%) in the 78 mg/m^2 cohort, 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 3 of 3 subjects (100%) in the 153 mg/m^2 cohort, and 1 of 1 subject (100%) in the 214 mg/m^2 cohort. Adverse events occurring at an incidence of ≥40% were pneumonia, febrile neutropenia, lymphopenia, hyperglycaemia, hypocalcaemia, hypokalaemia, constipation, diarrhoea, chills, and haemoglobin decreased (2 subjects each; 50.0%) in the 78 mg/m^2 cohort; pneumonia, anaemia, febrile neutropenia, hyperglycaemia, hypoalbuminaemia, hypocalcaemia, hypokalaemia, dyspnoea, nausea, APTT prolonged, ALT increased, haemoglobin decreased, neutrophil count decreased, platelet count decreased, and prothrombin level increased in (2 subjects each; 66.7%) in the 109 mg/m^2 cohort; hyperglycaemia, hypokalaemia, and electrocardiogram QT prolonged (3 subjects each; 100%); pneumonia, febrile neutropenia, neutropenia, hypoalbuminaemia, hyponatraemia, hypophosphataemia, insomnia, pleural effusion, diarrhoea, nausea, and blood alkaline phosphatase (ALP) increased (2 subjects each; 66.7%) in the 153 mg/m^2 cohort; and neutropenia, hypomagnesaemia, headache, cranial nerve disorder, nausea, and catheter site haemorrhage (1 subject each; 100%) in the 214 mg/m^2 cohort.

Serious adverse events occurred in 2 of 4 subjects (50.0%) in the 78 mg/m^2 cohort, 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 2 of 3 subjects (66.7%) in the 153 mg/m^2 cohort. (No serious adverse events occurred in the 214 mg/m^2 cohort.) Serious adverse events occurring in ≥2 subjects were febrile neutropenia (2 subjects; 50.0%) in the 78 mg/m^2 cohort, febrile neutropenia (2 subjects; 66.7%) in the 109 mg/m^2 cohort; and febrile neutropenia (2 subjects; 66.7%) in the 153 mg/m^2 cohort. Among these events, a causal relationship to darinaparsin could not be ruled out for febrile neutropenia (1 subject) in the 78 mg/m^2 cohort and febrile neutropenia (1 subject) in the 153 mg/m^2 cohort.

Adverse events led to treatment discontinuation of darinaparsin in 1 of 4 subjects (25.0%) in the 78 mg/m^2 cohort. (In the 109 mg/m^2, 153 mg/m^2, and 214 mg/m^2 cohorts, no adverse events led to treatment discontinuation.) There were no adverse events that led to treatment discontinuation of darinaparsin occurring in ≥2 subjects.

7.3.5 Foreign phase I study (Study SGL1002)

Adverse events occurred in 4 of 4 subjects (100%) in the 78 mg/m^2 cohort, 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 5 of 5 subjects (100%) in the 153 mg/m^2 cohort, 3 of 3 subjects (100%) in the 214 mg/m^2 cohort, 6 of 6 subjects (100%) in the 300 mg/m^2 cohort, 11 of 11 subjects (100%) in the 420 mg/m^2 cohort, 4 of 4 subjects (100%) in the 500 mg/m^2 cohort, and 4 of 4 subjects (100%) in the 588 mg/m^2 cohort. Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 1 of 4 subjects (25.0%) in the 78 mg/m^2 cohort, 2 of 3 subjects (66.7%) in the 109 mg/m^2 cohort, 2 of 5 subjects (40.0%) in the 153 mg/m^2 cohort, 2 of 3 subjects (66.7%) in the 214 mg/m^2 cohort, 2 of 6 subjects (33.3%) in the 300 mg/m^2 cohort, 5 of 11 subjects (45.5%) in the 420 mg/m^2 cohort, 3 of 4 subjects (75.0%) in the 500 mg/m^2 cohort, and 3 of 4 subjects (75.0%) in the 588 mg/m^2 cohort. Adverse events occurring at an incidence of ≥40% were dyspnoea (3 subjects; 75.0%); cough, myalgia, and fatigue (2 subjects each; 50.0%) in the 78 mg/m^2 cohort; headache, dyspnoea, constipation, nausea, and fatigue (2 subjects each; 66.7%) in the 109 mg/m^2 cohort; fatigue (5 subjects; 100%); dyspnoea and nausea (3 subjects each; 60.0%); infection, decreased appetite, abdominal tenderness, constipation, vomiting, and oedema peripheral (2 subjects each; 40.0%) in the 153 mg/m^2 cohort; fatigue (3 subjects; 100%); abdominal pain, nausea, and vomiting (2 subjects each; 66.7%) in the 214 mg/m^2 cohort; fatigue (4 subjects; 66.7%); nausea (3 subjects; 50.0%) in the 300 mg/m^2 cohort; fatigue (8 subjects; 72.7%); decreased appetite and nausea (5 subjects each; 45.5%) in the 420 mg/m^2 cohort; nausea and vomiting (3 subjects each; 75.0%); decreased appetite, confusional state, dizziness, speech disorder, hypotension, and fatigue (2 subjects each; 50.0%) in the 500 mg/m^2 cohort; constipation (3 subjects; 75.0%); and mental status changes, ataxia, diarrhoea, nausea, and pyrexia (2 subjects each; 50.0%) in the 588 mg/m^2 cohort.

Serious adverse events occurred in 3 of 4 subjects (75.0%) in the 78 mg/m^2 cohort, 1 of 3 subjects (33.3%) in the 109 mg/m^2 cohort, 1 of 5 subjects (20.0%) in the 153 mg/m^2 cohort, 2 of 3 subjects (66.7%) in the 214 mg/m^2 cohort, 2 of 6 subjects (33.3%) in the 300 mg/m^2 cohort, 2 of 11 subjects (18.2%) in the 420 mg/m^2 cohort, 4 of 4 subjects (100%) in the 500 mg/m^2 cohort, and 2 of 4 subjects (50.0%) in the 588 mg/m^2 cohort. Serious adverse events occurring in ≥2 subjects were dyspnoea (2 subjects; 50.0%) in the 78 mg/m^2 cohort; pneumonia (2 subjects; 18.2%) in the 420 mg/m^2 cohort; confusional state (2 subjects; 50.0%) in the 500 mg/m^2 cohort; mental status changes and ataxia (2 subjects each; 50.0%) in the 588 mg/m^2 cohort. (In the 109 mg/m^2, 153 mg/m^2, 214 mg/m^2, or 300 mg/m^2 cohorts, no serious adverse events occurred in ≥2 subjects.) Among these events, a causal relationship to darinaparsin could not be ruled out for confusional state (1 subject) in the 500 mg/m^2 cohort, and mental status changes and ataxia (2 subjects each) in the 588 mg/m^2 cohort. (In the 78 mg/m^2 and 420 mg/m^2 cohorts, there were no serious adverse events for which a causal relationship to darinaparsin could not be ruled out.)

Adverse events led to discontinuation of darinaparsin in 2 of 4 subjects (50.0%) in the 500 mg/m^2 cohort and 2 of 4 subjects (50.0%) in the 588 mg/m^2 cohort. (In the 420 mg/m^2 or lower dosage cohorts, no adverse events led to discontinuation of darinaparsin.) Adverse events leading to treatment

discontinuation of darinaparsin occurring in ≥2 subjects were mental status changes and ataxia (2 subjects each; 50.0%) in the 588 mg/m^2 cohort, and a causal relationship to darinaparsin could not be ruled out for either of the events. (In the 500 mg/m^2 cohort, there were no adverse events that led to discontinuation of darinaparsin occurring in ≥2 subjects.)

7.3.6 Foreign phase I/II study (Study SGL2001)

Adverse events occurred in 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 3 of 3 subjects (100%) in the 153 mg/m^2 cohort, 4 of 4 subjects (100%) in the 214 mg/m^2 cohort, 16 of 17 subjects (94.1%) in the 300 mg/m^2 cohort, 4 of 4 subjects (100%) in the 420 mg/m^2 cohort. Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 3 of 3 subjects (100%) in the 109 mg/m^2 cohort, 3 of 3 subjects (100%) in the 153 mg/m^2 cohort, 4 of 4 subjects (100%) in the 214 mg/m^2 cohort, 12 of 17 subjects (70.6%) in the 300 mg/m^2 cohort, and 4 of 4 subjects (100%) in the 420 mg/m^2 cohort. Adverse events occurring at an incidence of ≥40% were fatigue (3 subjects; 100%); urinary tract infection, headache, infusion site pain, and weight increased (2 subjects each; 66.7%) in the 109 mg/m^2 cohort; myalgia and infusion site pain (2 subjects each; 66.7%) in the 153 mg/m^2 cohort; nausea (4 subjects; 100%); vomiting and infusion site pain (3 subjects each; 75.0%); decreased appetite, constipation, pruritus, back pain, chills, fatigue, and pyrexia (2 subjects each; 50.0%) in the 214 mg/m^2 cohort; fatigue (8 subjects; 47.1%) in the 300 mg/m^2 cohort; fatigue (3 subjects; 75.0%); confusional state, dizziness, headache, and epistaxis (2 subjects; 50.0%) in the 420 mg/m^2 cohort.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 109 mg/m^2 cohort, 3 of 4 subjects (75.0%) in the 214 mg/m^2 cohort, 6 of 17 subjects (35.3%) in the 300 mg/m^2 cohort, and 2 of 4 subjects (50.0%) in the 420 mg/m^2 cohort. (In the 153 mg/m^2 cohort, no serious adverse events occurred.) Serious adverse events occurring in ≥2 subjects were confusional state (2 subjects; 11.8%) in the 300 mg/m^2 cohort, and a causal relationship to darinaparsin could not be ruled out in either of the subjects. (In the 109 mg/m^2, 214 mg/m^2, and 420 mg/m^2 cohorts, there were no serious adverse events that occurred in ≥2 subjects.)

Adverse events leading to treatment discontinuation of darinaparsin occurred in 1 of 3 subjects (33.3%) in the 109 mg/m^2 cohort, 6 of 17 subjects (35.3%) in the 300 mg/m^2 cohort, and 1 of 4 subjects (25.0%) in the 420 mg/m^2 cohort. (In the 153 mg/m^2 and 214 mg/m^2 cohorts, no adverse events leading to treatment discontinuation of darinaparsin occurred.) Adverse events leading to treatment discontinuation of darinaparsin that occurred in ≥2 subjects were disease progression (4 subjects; 23.5%) in the 300 mg/m^2 cohort, and a causal relationship to darinaparsin was denied in all of the subjects. (In the 109 mg/m^2 and 420 mg/m^2 cohorts, there were no adverse events leading to treatment discontinuation of darinaparsin that occurred in ≥2 subjects.)

7.3.7 Foreign phase II study (Study SGL2001b)

Adverse events occurred in 17 of 17 subjects (100%). Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 11 of 17 subjects (64.7%). Adverse events occurring at

an incidence of ≥20% of subjects were anaemia (12 subjects; 70.6%), nausea (8 subjects; 47.1%), fatigue (6 subjects; 35.3%), thrombocytopenia (5 subjects; 29.4%), hypercalcaemia, dizziness, constipation, and disease progression (4 subjects each; 23.5%).

Serious adverse events occurred in 8 of 17 subjects (47.1%). Serious adverse events occurring in ≥2 subjects were disease progression (4 subjects; 23.5%) and pain (2 subjects; 11.8%), and a causal relationship to darinaparsin was denied for all these events.

Adverse events leading to treatment discontinuation of darinaparsin occurred in 5 of 17 subjects (29.4%). There were no adverse events that led to treatment discontinuation of darinaparsin occurring in ≥2 subjects.

7.3.8 Foreign phase II study (Study SGL2003)

Adverse events occurred in 50 of 50 subjects (100%). Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 25 of 50 subjects (50.0%). Adverse events occurring at an incidence of ≥20% of subjects were pyrexia and anaemia (20 subjects each; 40.0%); diarrhoea (17 subjects; 34.0%); dyspnoea and decreased appetite (15 subjects each; 30.0%); nausea and disease progression (14 subjects each; 28.0%); vomiting and fatigue (13 subjects each; 26.0%); and thrombocytopenia (11 subjects; 22.0%).

Serious adverse events occurred in 28 of 50 subjects (56.0%). Serious adverse events occurring in ≥2 subjects were disease progression (13 subjects; 26.0%); dyspnoea (6 subjects; 12.0%); pneumonia (5 subjects; 10.0%); pyrexia (4 subjects; 8.0%); acute kidney injury and hypotension (3 subjects each; 6.0%); sepsis, respiratory failure, hypercalcaemia, leukocytosis, and fall (2 subjects each; 4.0%). Among these events, a causal relationship to darinaparsin could not be ruled out for fall (1 subject).

Adverse events led to treatment discontinuation of darinaparsin in 12 of 50 subjects (24.0%). Adverse events leading to treatment discontinuation of darinaparsin that occurred in ≥2 subjects were disease progression (9 subjects; 18.0%); and hypotension (2 subjects; 4.0%). A causal relationship to darinaparsin was denied for all these events.

7.3.9 Foreign phase II study (Study SGL2005)

Adverse events occurred in 13 of 15 subjects (86.7%). Adverse events for which a causal relationship to darinaparsin could not be ruled out occurred in 10 of 15 subjects (66.7%). Adverse events occurring at an incidence of ≥20% of subjects were decreased appetite and vomiting (7 subjects each; 46.7%); nausea and fatigue (6 subjects each; 40.0%); anaemia, insomnia, abdominal distension, abdominal pain, ascites, constipation, diarrhoea, dry mouth, pyrexia, AST increased, weight increased, and fall (3 subjects each; 20.0%).

Serious adverse events occurred in 5 of 15 subjects (33.3%). The reported serious adverse events were disease progression (2 subjects); dehydration, decreased appetite, confusional state, somnolence, diarrhoea, gastrointestinal haemorrhage, nausea, and vomiting (1 subject each; 6.7%). A causal relationship to darinaparsin was denied for all these events.

Adverse events led to treatment discontinuation of darinaparsin in 3 of 15 subjects (20.0%). The reported adverse events leading to treatment discontinuation of darinaparsin were dehydration, gastrointestinal haemorrhage, and AST increased (1 subject each; 6.7%). Among these events, a causal relationship to darinaparsin could not be ruled out for AST increased (1 subject).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that darinaparsin has a certain level of efficacy in the treatment of relapsed or refractory PTCL, and that darinaparsin has acceptable safety in view of its benefits. Darinaparsin is a drug with a new active ingredient and causes decreases in mitochondrial membrane potential and other effects, enhancing production of intracellular ROS, which together with other factors, are thought to induce apoptosis and cell cycle arrest, thereby exerting antitumor effects. Darinaparsin is clinically meaningful because it offers a new treatment option for patients with relapsed or refractory PTCL. PMDA considers that several issues including the efficacy, safety, and clinical positioning require further discussion.

PMDA has concluded that darinaparsin may be approved if darinaparsin is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 12, 2022

Product Submitted for Approval

Brand Name	Darvias Injection 135 mg
Non-proprietary Name	Darinaparsin
Applicant	Solasia Pharma K.K.
Date of Application	June 30, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Efficacy

As discussed in Section "7.R.2 Efficacy" in Review Report (1), the overall response rate by central review according to the Revised RC, the primary endpoint, and its 90% confidence interval was 19.3% [11.2, 29.9] (11 of 57 subjects) in the global phase II study (Study 02) in patients with relapsed or refractory PTCL. PMDA concluded that this result, which exceeded the prespecified threshold response rate of 10%, together with other data, demonstrated that darinaparsin has a certain level of efficacy in the treatment of patients with relapsed or refractory PTCL.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.2 Safety

In view of the discussions presented in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that the adverse events of special interest during treatment with darinaparsin are myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous disorders, and QT interval prolongation.

Although the use of darinaparsin requires caution particularly for the adverse events listed above, PMDA concluded that patients should be able to tolerate darinaparsin provided that appropriate steps including monitoring and control of adverse events, dose interruption/reduction, and treatment discontinuation are

taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.3 Clinical positioning and indication

In view of the discussions presented in Section "7.R.4 Clinical positioning and indication" in Review Report (1), PMDA concluded that darinaparsin should be indicated for "relapsed or refractory peripheral T-cell lymphoma" as proposed by the applicant, provided that the "Clinical Studies" section of the package insert includes descriptions regarding histological subtypes of patients eligible for Study 02 and those of patients who were actually enrolled, together with efficacy results by histological subtype, and that a statement to the effect of the following is included in the "Precautions Concerning Indications" section.

Precautions Concerning Indications

- Diagnosis of disease suitable for darinaparsin treatment should be performed by physicians or at medical institutions with sufficient experience in diagnostic pathology.
- Whether a patient is suitable for treatment with darinaparsin should be decided only after becoming fully familiar with the details in the "Clinical Studies" section regarding histological subtypes of patients who were enrolled in the clinical studies, and gaining a thorough understanding of the efficacy and safety of darinaparsin.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

1.4 Dosage and administration

In view of discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections should be appropriately specified as shown below:

Dosage and Administration

The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over 1 hour for 5 days, followed by a 16-day rest period. This 21-day treatment cycle should be repeated. The dose may be reduced, as appropriate, according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of darinaparsin in combination with other antineoplastic agents have not been established.
- Criteria for dose interruption, etc. due to adverse reactions

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above.

On the basis of the above, PMDA instructed the applicant to specify the “Dosage and Administration” and the “Precautions Concerning Dosage and Administration” sections as shown above. The applicant agreed with the instruction.

1.5 Risk management plan (draft)

The applicant intends to conduct post-marketing surveillance covering all patients who received darinaparsin to evaluate various aspects of darinaparsin including safety in clinical use. The proposed safety specification includes psychiatric disorders, nervous system disorders, and cardiac disorders (e.g., QT interval prolongation), as well as safety in patients with renal impairment, and use in patients with hepatic impairment, and a planned sample size of 70 patients and a follow-up period of 6 cycles (18 weeks) have been specified.

In view of the discussions presented in Section “7.R.6 Post-marketing investigations” in Review Report (1), PMDA concluded that post-marketing surveillance should cover all patients who received darinaparsin for a specified period after the product launch, to gather data in an unbiased manner without delay, and the safety data so obtained should be provided promptly to healthcare professionals.

PMDA also concluded that the post-marketing surveillance plan should be as follows:

- The safety specification for the post-marketing surveillance should be myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, peripheral nervous system disorders, and QT interval prolongation.
- The planned sample size for the post-marketing surveillance should be reconsidered after examining the clinical study data including the incidence of the adverse events that are to be included in the safety specification.
- The follow-up period should be longer than 6 cycles (18 weeks).

At the Expert Discussion, the expert advisors supported the PMDA’s conclusion shown above.

On the basis of the above discussions, PMDA instructed the applicant to reconsider the post-marketing surveillance plan.

The applicant’s response:

- The safety specification for the post-marketing surveillance will be myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, QT interval prolongation, and peripheral nervous system disorders.
- The planned sample size and follow-up period for the post-marketing surveillance were reconsidered after examining the clinical study data including the incidence of the adverse events that are to be included in the safety specification, and a planned sample size of 80 patients and a follow-up period of 9 cycles (27 weeks) are specified.

PMDA accepted the applicant's response.

In view of the discussions above, PMDA concluded that the risk management plan (draft) for darinaparsin should include the safety specification presented in Table 30, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 31 and Table 32, respectively.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelosuppression • Infections • Psychiatric disorders (e.g., delirium and confusion) • Central nervous system disorders • QT interval prolongation	• Peripheral nervous system disorders	None
Efficacy specification		
None		

Table 31. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey (all-case surveillance)	None	• Disseminate data gathered during early post-marketing phase vigilance • Prepare and disseminate information materials for healthcare professionals

Table 32. Outline of use-results survey (draft)

Objective	To investigate the safety and other aspects of darinaparsin in clinical use after market launch
Survey method	All-case surveillance
Population	All patients receiving darinaparsin
Observation period	9 cycles (27 weeks)
Planned sample size	80 patients
Main survey items	Safety specification: myelosuppression, infections, psychiatric disorders (e.g., delirium and confusion), central nervous system disorders, peripheral nervous system disorders, and QT interval prolongation Other main survey items: patient characteristics (e.g., age, body weight, sex, histological subtype, medical history, complications, prior therapy, presence/absence of renal impairment), darinaparsin treatment status, adverse events, coadministered drugs

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following approval conditions provided that the prescribed precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after market launch, and that darinaparsin is properly used under the supervision of physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies at medical institutions with adequate facilities to respond to emergencies. Since darinaparsin is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug substance and drug product are both classified as powerful drugs.

Indication

Relapsed or refractory peripheral T-cell lymphoma

Dosage and Administration

The usual adult dosage is 300 mg/m^2 (body surface area) of darinaparsin administered once daily as an intravenous infusion over 1 hour for 5 days, followed by a 16-day rest period. This 21-day treatment cycle should be repeated. The dose may be reduced, as appropriate, according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of patients are collected to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Warnings

Darinaparsin should be administered only to patients who are considered suitable for its use under the supervision of physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies at medical institutions with adequate facilities to respond to emergencies. Prior to the start of treatment, the benefits and potential risks of the treatment should be thoroughly explained to patients or their family members, and consent must be obtained.

Contraindications

1. Patients with a history of hypersensitivity to Darvias or any of the excipients
2. Pregnant women or women who may be pregnant

Precautions Concerning Indications

1. Diagnosis of disease suitable for darinaparsin treatment should be performed by physicians or at medical institutions with sufficient experience in diagnostic pathology.
2. Whether a patient is suitable for treatment with darinaparsin should be decided only after becoming fully familiar with the details in the "Clinical Studies" section regarding histological subtypes of patients who were enrolled in the clinical studies, and gaining a thorough understanding of the efficacy and safety of darinaparsin.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of darinaparsin in combination with other antineoplastic agents have not been established.

2. If the patient develops an adverse reaction following administration of darinaparsin, the dose of darinaparsin must be interrupted, reduced, or treatment with darinaparsin must be discontinued based on the following criteria:

Criteria for dose interruption, reduction, treatment discontinuation due to adverse reactions

Adverse reaction	Action
Grade 1 or 2* psychiatric disorders such as delirium and confusion, central nervous system disorders	Interrupt doses until symptoms resolve. After symptoms resolve, treatment may be resumed at the same dose level.
Grade 3* adverse reactions (excluding nausea/vomiting, diarrhoea, and clinically irrelevant asymptomatic abnormal laboratory values)	Interrupt doses until recovery to Grade 1 or to the grade before the start of treatment. After adverse reactions resolve, treatment may be resumed at a reduced dose level of 200 mg/m^2. If adverse reactions recur after dose reduction to 200 mg/m^2, discontinue treatment.
Grade 3* nausea/vomiting, diarrhoea	If symptoms do not resolve by symptomatic therapy, interrupt doses until they resolve. After symptoms resolve, treatment may be resumed at a reduced dose level of 200 mg/m^2. If adverse reactions recur after dose reduction to 200 mg/m^2, discontinue treatment.
Grade 4* adverse reactions (excluding clinically irrelevant asymptomatic abnormal laboratory values)	Discontinue treatment.

*, The grades are in accordance with the NCI-CTCAE v4.0.

Appendix

List of Abbreviations

AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APL	acute promyelocytic leukemia
application	marketing application
APTT	activated partial thromboplastin time
^{76}As-labeled darinaparsin	^{76}As-radiolabeled darinaparsin
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BID	bis in die
CI	confidence interval
CM-H_2DCFDA	5,6-carboxy-2',7'-dichlorofluorescein-diacetate
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CRu	complete response unconfirmed
CTCL	cutaneous T-cell lymphoma
CYP	cytochrome P450
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
dP/dt_{max}	maximum rate of rise of left ventricular pressure
dP/dt_{min}	minimum rate of rise of left ventricular pressure
EBV	Epstein-Barr virus
efflux ratio	the ratio of permeability coefficient in the secretory direction to that in the absorptive direction
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FEP	fluorinated ethylene propylene copolymer
FGFb	fibroblast growth factor beta
Forodesine	forodesine hydrochloride
GC	gas chromatography
HBV	hepatitis B virus
HEPES	4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid
hERG	human *ether-a-go-go* related gene
HLGT	high level group term
HLT	high level term
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography-mass spectrometry
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use

Initial Risk Assessment Report on Chemical Substances	National Institute of Technology and Evaluation, Initial Risk Assessment Report on Chemical Substances ver.1.0: No.130 Arsenic and Its Inorganic Compounds, 2008 [in Japanese]
IR	infrared absorption spectroscopy
$K_{I, app}$	apparent inhibitor concentration at 50% of maximum inhibition rate
k_{inact}	maximum inactivation rate constant
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	master file
MM	multiple myeloma
MPE	mean photo effect
mPTP	mitochondrial permeability transition pore
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in T-cell Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PAR	proven acceptable range
PD	progressive disease
P-gp	P-glycoprotein
PI	propidium iodide
PIF	photo irritation factor
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PT	preferred term
PTCL	peripheral T-cell lymphoma
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
QD	quaque die
Revised RC	Revised Response Criteria for Malignant Lymphoma
ROS	reactive oxygen species
SCID mouse	severe combined immunodeficiency mouse
SD	stable disease
SOC	system organ class
Study 01	Study SP-02L01
Study 02	Study SP-02L02
Study 03	Study SP-02L03
T-ALL	acute T-lymphoblastic leukemia
TK	toxicokinetics
T_{P-E} interval	T-peak to T-end interval
UV	ultraviolet spectroscopy
UVA	ultraviolet A
VZV	varicella zoster virus

WHO	World Health Organization
γ-GT	γ-glutamyl transpeptidase
ΔQTcF	change from baseline in QT interval corrected with Fridericia's formula