Review Report

November 5, 2019
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	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination) (JAN*)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	March 29, 2019
Dosage Form/Strength	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination)
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 267 of 2012 [*24 yaku*]; PSEHB/PED Notification No. 0319-1 dated March 19, 2012: Orphan Drug Designation No. 427 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0304-1 dated March 4, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of CD30-positive Hodgkin's lymphoma and 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 condition. The occurrence of neuropathy peripheral, bone marrow depression (neutropenia), and lung disorders should be further investigated via post-marketing surveillance.

Indications	The following CD30-positive diseases: ○Hodgkin's lymphoma ○Peripheral T-cell lymphoma

~~㋑Relapsed or refractory anaplastic large-cell lymphoma~~

(Underline denotes additions and strikethrough denotes deletions.)

Dosage and Administration

1. Previously untreated CD30-positive Hodgkin's lymphoma

   In combination with doxorubicin hydrochloride, vinblastine sulfate, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

2. Previously untreated CD30-positive peripheral T-cell lymphoma

   In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient's condition.

3. Relapsed or refractory CD30-positive Hodgkin's lymphoma and peripheral T-cell lymphoma ~~anaplastic large-cell lymphoma~~

   The usual ~~adult~~ dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

(Underline denotes additions and strikethrough denotes deletions.)

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

September 25, 2019

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	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	March 29, 2019
Dosage Form/Strength	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination)
Proposed Indications	The following CD30-positive diseases: ○Hodgkin's lymphoma ○Peripheral T-cell lymphoma ~~○Relapsed or refractory anaplastic large-cell lymphoma~~ (Underline denotes additions and strikethrough denotes deletions.)

Proposed Dosage and Administration

1. Adults

~~1.~~ Previously untreated CD30-positive Hodgkin's lymphoma

In combination with doxorubicin hydrochloride, vinblastine sulfate, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

Previously untreated CD30-positive peripheral T-cell lymphoma

In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient's condition.

~~2.~~ Relapsed or refractory CD30-positive Hodgkin's lymphoma and peripheral T-cell lymphoma ~~anaplastic large-cell lymphoma~~

The usual adult dosage is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3

weeks. The dose may be reduced as appropriate according to the patient's condition.

2. Children

Relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma

The usual dosage for young children and children is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

(Underline denotes additions and strikethrough denotes deletions.)

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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

CD30 is a type I transmembrane protein belonging to the tumor necrosis factor receptor superfamily. CD30 is expressed on Reed-Sternberg cells of Hodgkin's lymphoma (HL) and T-cells inducing other T-cell lymphoproliferative diseases.

Brentuximab Vedotin (INN, brentuximab vedotin) is an antibody-drug conjugate discovered by Seattle Genetics, Inc. (the US). Brentuximab vedotin is composed of a chimeric monoclonal antibody, which contains variable regions derived from a mouse anti-human CD30 antibody, constant regions derived from a human immunoglobulin G1 (IgG1), and monomethyl auristatin E (MMAE), a tubulin polymerization inhibitor. MMAE is covalently bound to the chimeric monoclonal antibody via a linker containing a maleimide, caproyl spacer, valine, citrulline, and *p*-aminobenzyloxy carbonyl group. After binding to CD30 on the cell surface, brentuximab vedotin is internalized via CD30 in the form of an antibody-drug conjugate. Within the cell, MMAE, which is released by proteolytic cleavage, inhibits tumor proliferation by inducing cell cycle arrest and apoptosis.

In Japan, brentuximab vedotin was approved in January 2014 for the indication described as "the following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma," and in September 2018 for the indication described as "the following CD30-positive diseases: Hodgkin's lymphoma, relapsed or refractory anaplastic large-cell lymphoma."

1.2 Development history etc.

In the clinical development of brentuximab vedotin for the treatment of patients with peripheral T-cell lymphoma (PTCL), Seattle Genetics, Inc. (the US) initiated a foreign phase I study in patients with previously untreated CD30-positive PTCL (Study 011) in February 2011. Subsequently, a global phase III study in patients with previously untreated CD30-positive PTCL (Study 014) started in January 2013, and a foreign phase II study in patients with relapsed or refractory CD30-positive non-Hodgkin's lymphoma (NHL) (Study 012) in August 2011.

In the clinical development of brentuximab vedotin for the treatment of children with relapsed or refractory HL and anaplastic large cell lymphoma (ALCL), Millennium Pharmaceuticals, Inc. (in the US) initiated a foreign phase I/II study in patients with relapsed or refractory HL or systemic ALCL (sALCL)[1)] (Study C25002) in April 2012.

In the US, an application for approval of brentuximab vedotin was filed in October 2018 for the treatment of previously untreated CD30-positive PTCL, with the results of Study 014 as pivotal clinical data. Brentuximab vedotin was approved in November 2018 for the following indication: "ADCETRIS is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing PTCL, including

1) The phase I part of the study enrolled patients with relapsed or refractory CD30-positive hematologic malignancies.

angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone." In the EU, an application for approval of brentuximab vedotin was filed in [redacted], 20[redacted] for the treatment of previously untreated CD30-positive PTCL, with the results of Study 014 as pivotal clinical data. The application is currently under review.

As of August 2019, only the US has approved brentuximab vedotin for the treatment of previously untreated CD30-positive PTCL. No countries or regions have approved brentuximab vedotin for the indication of relapsed or refractory CD30-positive PTCL, or for the dosage regimen for children with relapsed or recurrent CD30-positive HL or ALCL.

In Japan, as part of the clinical development of brentuximab vedotin for the treatment of PTCL, the applicant started patient enrollment in Study 014 in [redacted], 20[redacted]. The clinical development of brentuximab vedotin for children with relapsed or refractory HL or ALCL began with an investigator-initiated study conducted from [redacted], 20[redacted] by the National Hospital Organization Nagoya Medical Center, as a phase I study in patients with relapsed or refractory CD30-positive HL or sALCL (Study BV-HLALCL) under the support of the Project Promoting Clinical Trials for Development of New Drugs of the Japan Agency for Medical Research and Development (AMED).

With pivotal data from Studies 014, BV-HLALCL, and C25002, the applicant has recently filed a partial change application for brentuximab vedotin to add an indication and dosage for patients with CD30-positive PTCL, and dosage for children with relapsed or refractory CD30-positive HL or ALCL. The applicant also submitted the results of Study 012 during the course of the approval review.

Brentuximab vedotin was designated as an orphan drug in (a) March 2019 and (b) March 2012 with the intended indications of (a) "CD30-positive peripheral T-cell lymphoma" (Orphan Drug Designation No. 427 [*31 yaku*]) and (b) "CD30-positive HL and ALCL" (Orphan Drug Designation No. 267 [*24 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and new dosage, no additional data on the quality of brentuximab vedotin were submitted.

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

The present application is intended for a new indication and new dosage, and non-clinical pharmacology of brentuximab vedotin was evaluated for the initial approval. Therefore, no new non-clinical pharmacological data were submitted.

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

The present application is intended for a new indication and new dosage, and non-clinical pharmacokinetics of brentuximab vedotin were evaluated for the initial approval. Therefore, no new non-clinical pharmacokinetic data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and new dosage, no toxicity data of brentuximab vedotin were submitted.

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

The present application is intended for a new indication and new dosage, and biopharmaceutic studies and associated analytical methods for brentuximab vedotin were evaluated during for the initial approval. Therefore, no new data on biopharmaceutic studies and associated analytical methods were submitted.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of brentuximab vedotin in cancer patients was evaluated for use as a monotherapy and in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

6.1.1 Japanese phase I study (CTD 5.3.5.2-3, Study BV-HLALCL [ongoing since [redacted], 20[redacted], data cutoff on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted in 6 patients with relapsed or refractory CD30-positive HL or sALCL aged from ≥2 to <18 years to evaluate the PK, etc. of brentuximab vedotin. All 6 patients were included in the PK analyses.

Brentuximab vedotin 1.8 mg/kg was intravenously administered every 3 weeks, and serum brentuximab vedotin concentration, plasma MMAE concentration, etc. were assessed. The formation of antibodies against brentuximab vedotin was not assessed.

Tables 1 and 2 show the PK parameters of brentuximab vedotin and MMAE on Days 1 and 22 (the first and second doses).

Table 1. PK parameters of brentuximab vedotin

Day	C_{max} (μg/mL)	AUC_{21day} (μg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
1	28.8 (25.9)	71.2 (29.5)	4.54 (37.7)	0.797 (39.3)	4.40 (39.3)
22	29.8 (9.05)	62.1 (46.5)	5.10 (56.8)	0.971 (98.8)	5.22 (36.5)

Geometric mean (coefficient of variation %); N = 6

Table 2. PK parameters of MMAE

Day	C_{max} (ng/mL)	t_{max*} (day)	AUC_{21day} (ng·day/mL)	$t_{1/2}$ (day)
1	2.79 (34.7)	2.95 (1.02, 3.02)	18.6 (29.6)	2.82 (14.4)
22	2.19 (42.4)	2.96 (0.983, 3.01)	13.7 (40.9)	3.39 (7.54)

Geometric mean (coefficient of variation %); N = 6; * median (range)

6.1.2 Foreign phase I study (CTD 5.3.5.2-1, Study 011 [February 2011 to May 2017])

An open-label uncontrolled study was conducted in 39 patients with previously untreated CD30-positive PTCL aged ≥18 years[2)] to evaluate the PK, etc. of brentuximab vedotin. All 39 patients were subjected to the PK analyses.

Each treatment cycle consisted of 21 days. In Arm 1, brentuximab vedotin 1.8 mg/kg was intravenously administered on Day 1 of Cycles 1 and 2, and CHOP[3)] was administered in Cycle 3 and subsequent cycles, followed by resumed brentuximab vedotin 1.8 mg/kg after the completion of CHOP treatment. In Arms 2 and 3, brentuximab vedotin 1.8 mg/kg was intravenously administered in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).[4)] Unless patients experienced disease progression or met the discontinuation criteria, CHOP treatment in Arm 1 and CHP treatment in Arms 2 and 3 were continued for up to 6 cycles, and brentuximab monotherapy was continued for up to 10 cycles in Arms 1, 2, and 3.

The plasma brentuximab vedotin concentrations and plasma MMAE concentrations are shown in Table 3.

Among 17 patients who were assessed for the formation of anti-brentuximab vedotin antibodies, 7 (41%) tested positive for the antibodies. Neutralizing antibodies were not determined.

Table 3. Serum brentuximab vedotin concentrations (μg/mL) and plasma MMAE concentrations (ng/mL)

Analyte	Timepoint	Arm 1		Arm 2		Arm 3	
		N	Concentration	N	Concentration	N	Concentration
Brentuximab vedotin	Completion of the Cycle 1 dose	13	35 (18)	5	29 (26)	-	-
	Day 2 of Cycle 1	13	14 (29)	5	8.3 (52)	-	-
	Before the Cycle 2 dose	9	0.38 (63)	5	0.21 (80)	-	-
	Before the Cycle 10 dose	9	0.51 (130)	3	1.0 (64)	12	1.2 (78)
	Before the Cycle 11 dose	11	0.79 (67)	4	1.0 (53)	12	1.1 (87)
	Before the Cycle 12 dose	10	0.99 (50)	3	1.6 (22)	10	1.3 (72)
MMAE	Completion of the Cycle 1 dose	13	0.15 (51)	5	0.22 (90)	-	-
	Day 2 of Cycle 1	13	3.7 (46)	5	4.9 (150)	-	-
	Before the Cycle 2 dose	11	0.12 (59)	4	0.053 (110)	-	-
	Before the Cycle 10 dose	8	0.11 (64)	3	0.058 (41)	11	0.091 (35)
	Before the Cycle 11 dose	11	0.085 (63)	4	0.074 (25)	10	0.093 (59)
	Before the Cycle 12 dose	10	0.11 (58)	3	0.092 (54)	10	0.070 (55)

Geometric mean (coefficient of variation %); -, not measured

6.1.3 Foreign phase I/II study (CTD 5.3.5.2-2, Study C25002 [April 2012 to May 2018])

An open-label uncontrolled study was conducted in 36 patients with relapsed or refractory HL or sALCL, aged ≥2 to <18 years[5)] to evaluate the PK, etc. of brentuximab vedotin. Of these 36 patients, 33 were subjected to the PK analyses.

2) Of these 39 patients, 13 were treated in Arm 1, 6 in Arm 2, and 20 in Arm 3, and all the patients in each arm were used for the PK analyses.
3) Cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (up to 2 mg/dose) were intravenously administered on Day 1, and prednisone (unapproved in Japan) 100 mg was orally administered on Days 1 to 5.
4) Cyclophosphamide 750 mg/m^2 and doxorubicin 50 mg/m^2 were intravenously administered on Day 1, and prednisone (unapproved in Japan) 100 mg was orally administered on Days 1 to 5.
5) The study enrolled patients with sALCL aged ≥2 to <18 years, and those with HL aged ≥5 to <18 years.

Brentuximab vedotin 1.4 or 1.8 mg/kg was intravenously administered every 3 weeks, and serum brentuximab vedotin concentration, plasma MMAE concentration, etc. were assessed.

The PK parameters of brentuximab vedotin and MMAE on Day 1 and Day 148 (the first and eighth doses of brentuximab vedotin, respectively) are shown in Table 4 and Table 5, respectively.

Among 34 patients assessed for the formation of anti-brentuximab vedotin antibody, 14 (41%) were positive for the antibody, and 9 of these 14 patients were positive for neutralizing antibodies.

Table 4. PK parameters of brentuximab vedotin

Dose (mg/kg)	Day	N	C_{max} (μg/mL)	AUC_{21day} (μg·day/mL)	$t_{1/2}$ (day)	CL (L/day)	V_z (L)
1.4	1	3	22.9 (15.0)	50.3 (22.8)	3.88, 4.71[*1]	1.09, 1.58[*1]	5.64, 7.94[*1]
1.8	1	30	31.8 (28.5)	63.3 (31.3)[*2]	4.73 (34.1)[*3]	1.16 (36.0)[*3]	6.33 (39.5)[*3]
	148	14	33.7 (29.9)	98.0 (48.2)[*4]	7.34 (22.0)[*5]	0.818 (44.6)[*4]	7.35 (31.2)[*5]

Geometric mean (coefficient of variation %) (individual values for N = 2); *1, N = 2; *2, N = 26; *3, N = 25; *4, N = 13; *5, N = 11

Table 5. PK parameters of MMAE

Dose (mg/kg)	Day	N	C_{max} (ng/mL)	t_{max}[*1] (day)	AUC_{21day} (ng·day/mL)	$t_{1/2}$ (day)
1.4	1	3	4.45 (57.5)	1.94 (0.994, 3.85)	22.8 (29.8)	2.69, 3.40[*2]
1.8	1	32	4.39 (67.3)	1.87 (0.740, 3.98)	27.0 (60.9)[*3]	3.15 (28.5)[*4]
	148	13	2.01 (56.6)	2.02 (0.899, 4.05)	14.9 (57.1)[*5]	3.90 (12.3)[*6]

Geometric mean (coefficient of variation %) (individual values for N = 2); *1, median (range); *2, N = 2; *3, N = 27; *4, N = 22; *5, N = 10; *6, N = 5

6.1.4 Relationships between exposure, and efficacy and safety

Based on the results of a global phase III study (Study 014), the relationship between exposure to brentuximab vedotin (trough concentration) and efficacy or safety, and the relationship between exposure to MMAE (trough concentration) and safety were investigated.

6.1.4.1 Relationship between exposure and efficacy

The patients were divided into quartile groups[6)] based on trough brentuximab vedotin concentration[7)] to estimate progression-free survival (PFS) in each group using the Kaplan-Meier method. The results showed no significant correlation between trough brentuximab vedotin concentration and PFS.

6.1.4.2 Relationship between exposure and safety

The patients were divided into quartile groups[6)] based on trough brentuximab vedotin concentration[7)] to investigate the relationship between trough brentuximab vedotin concentration and the incidences of febrile neutropenia, Grade ≥2 peripheral neuropathy, Grade ≥4 neutropenia, or Grade ≥3 adverse events. Similarly, the patients were divided into quartile groups[8)] based on trough MMAE concentration[7)] to investigate the

6) The trough brentuximab vedotin concentration (μg/mL) in each quartile group ranged between ≥0 and ≤0.6095, >0.6095 and ≤0.909, >0.909 and ≤1.186, and >1.186 and ≤2.3, respectively.
7) The brentuximab vedotin concentration before the Day 1 dose of Cycle 4 (Each treatment cycle consisted of 21 days.)
8) The trough MMAE concentration (ng/mL) in each quartile group ranged between ≥0 and ≤0.067, >0.067 and ≤0.099, >0.099 and ≥0.149, and >0.149 and ≤0.7, respectively.

relationships between trough MMAE concentration and the incidences of each adverse event mentioned. The incidences of febrile neutropenia, Grade ≥4 neutropenia, and Grade ≥3 adverse events tended to be higher in the 2 groups with a higher trough MMAE concentration than in the 2 groups with a lower trough MMAE concentration. In contrast, no clear relationships were found between trough brentuximab vedotin concentration and the incidence of any of the above adverse events, or between trough MMAE concentration and the incidence of Grade ≥2 peripheral neuropathy.

6.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the subsections below, PMDA concluded that the applicant's explanation about the clinical pharmacology of brentuximab vedotin was acceptable.

6.R.1 Differences in PK between pediatric and adult patients and differences in pediatric PK between Japanese and non-Japanese patients

The applicant's explanation about (a) the differences in the PK of brentuximab vedotin and MMAE between children and adults, and (b) the differences in the pediatric PK of brentuximab vedotin and MMAE between Japanese and non-Japanese patients:

(a) Differences in the PK of brentuximab vedotin and MMAE between children and adults

The following observations indicate no clear differences in the PK of brentuximab vedotin or MMAE between children and adults.

- In a Japanese phase I/II study (Study TB-BC010088), the geometric mean (coefficient of variation [CV] %) C_{max}, AUC_{21day}, and $t_{1/2}$ values of (i) brentuximab vedotin and (ii) MMAE on Day 1 in patients aged ≥20 years who received intravenous doses of brentuximab vedotin 1.8 mg/kg were (i) 31.5 (9.6) μg/mL, 66.8 (1.5) μg·day/mL, and 7.42 (49) days, respectively, and (ii) 3.59 (50) ng/mL, 22.8 (43) ng·day/mL, and 3.57 (12) days, respectively (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013"). These results did not differ markedly from the $C_{max,}$ AUC_{21day}, and $t_{1/2}$ values for brentuximab vedotin and MMAE observed on Day 1 in patients aged ≥2 to <18 years who received intravenous doses of brentuximab vedotin 1.8 mg/kg in a Japanese phase I study (Study BV-HLALCL) [see Section 6.1.1].
- In a foreign phase I study (Study SG035-0001), the geometric mean (CV %) C_{max}, AUC_{21day}, and $t_{1/2}$ values of (i) brentuximab vedotin and (ii) MMAE observed on Day 1 in patients aged ≥18 years who received intravenous doses of brentuximab vedotin 1.8 mg/kg were (i) 32.0 (29) μg/mL, 76.7 (31) μg·day/mL, and 4.43 (38) days, respectively, and (ii) 4.97 (43) ng/mL, 36.1 (47) ng·day/mL, and 3.60 (25) days, respectively (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013"). These results did not differ markedly from the $C_{max,}$ AUC_{21day}, and $t_{1/2}$ values for brentuximab vedotin and MMAE observed on Day 1 in patients aged ≥2 to <18 years who received intravenous doses of brentuximab vedotin 1.8 mg/kg in a foreign phase I/II study (Study C25002) [see Section 6.1.3].

(b) Differences in the pediatric PKs of brentuximab vedotin and MMAE between Japanese and non-Japanese patients

The $C_{max,}$ AUC_{21day}, and $t_{1/2}$ values of brentuximab vedotin or MMAE on Day 1 in patients aged ≥2 to <18 who received intravenous doses of brentuximab vedotin 1.8 mg/kg in a Japanese phase I study (Study BV-HLALCL) did not clearly differ from those observed in a foreign phase I/II study (Study C25002) [see Sections 6.1.1 and 6.1.3]. Thus, there are no clear differences in the pediatric PKs of brentuximab vedotin or MMAE between Japanese and non-Japanese patients.

PMDA accepted the applicant's explanation.

6.R.2 Pharmacokinetic interactions with cyclophosphamide, doxorubicin, and prednisolone

The applicant's explanation:

In view of the following observations, neither brentuximab vedotin nor MMAE is likely to cause a pharmacokinetic interaction with concomitant drugs i.e., cyclophosphamide, doxorubicin, and prednisolone (CHP).

- A foreign phase I study (Study 011) showed no clear differences in serum brentuximab vedotin concentration or plasma MMAE concentration between brentuximab vedotin administered alone and that administered in combination with CHP [see Section 6.1.2]. Furthermore, doxorubicin was demonstrated to have no effects on the PK of brentuximab vedotin or MMAE (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated August 3, 2018").
- Neither brentuximab vedotin nor MMAE is likely to affect the PK of cyclophosphamide or prednisolone because (a) the antibody moiety of brentuximab vedotin is thought to be eliminated through proteolysis; (b) MMAE is unlikely to mediate pharmacokinetic interactions by inhibiting or inducing CYP isozymes, in clinical use of brentuximab vedotin (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013"). Furthermore, brentuximab vedotin and MMAE were demonstrated to have no effects on the PK of doxorubicin (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated August 3, 2018").

PMDA's view:

The applicant's explanation is generally acceptable. However, because of the lack of clinical study data on the pharmacokinetic interactions between brentuximab vedotin or MMAE and cyclophosphamide or prednisolone, the applicant should continue to collect information on the relevant pharmacokinetic interactions from various sources including published literature.

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

The applicant submitted efficacy and safety evaluation data from the following 5 clinical studies: a Japanese phase I study, a global phase III study, a foreign phase I study, a foreign phase I/II study, and a foreign phase II study (Table 6). The applicant also submitted the results of a Japanese phase I/II study (Table 6) as reference data.

Table 6. Clinical studies for efficacy and safety

Data type	Region	Study identifier	Phase	Subjects	No. of patients enrolled	Outline of dosage regimen	Main endpoints
Evaluation data	Japan	BV-HLALCL	I	Patients with relapsed or refractory CD30-positive HL or sALCL, aged ≥2 to <18 years	6	Intravenous brentuximab vedotin 1.8 mg/kg every 3 weeks	Safety PK
	Global	014	III	Patients with previously untreated CD30-positive PTCL	452 (a) 226 (b) 226	In 21-day cycles, (a) in combination with CHP, intravenous brentuximab vedotin on Day 1 of each cycle (for 6 to 8 cycles) (b) CHOP (for 6 to 8 cycles)	Efficacy Safety
	Foreign	011	I	Patients with previously untreated CD30-positive PTCL	39 Arm 1: 20 Arm 2: 6 Arm 3: 13	In 21-day cycles, Arm 1: intravenous brentuximab vedotin 1.8 mg/kg on Day 1 of Cycles 1 and 2, followed by CHOP in Cycle 3 onward (up to 14 cycles) Arms 2 and 3: in combination with CHP, intravenous brentuximab vedotin 1.8 mg/kg on Day 1 of each cycle (up to 16 cycles)	Safety PK
		C25002	I/II	Patients with relapsed or refractory HL or sALCL, aged ≥2 or ≥5 to <18 years	36	Intravenous brentuximab vedotin 1.4 or 1.8 mg/kg every 3 weeks (up to 16 doses)	Safety Efficacy PK
		012	II	Patients with relapsed or refractory CD30-positive NHL	Part A: 103 Part B: 16 Part C: 53	Intravenous brentuximab vedotin 1.8 mg/kg every 3 weeks in combination with RIT (in Part B) or without RIT (in Parts A and C)	Efficacy Safety PK
Reference data	Japan	TB-BC010088	I/II	Patients with relapsed or refractory CD30-positive HL or sALCL	20	Intravenous brentuximab vedotin 1.2 or 1.8 mg/kg every 3 weeks	Safety

The following subsections present summaries of each clinical study. Major adverse events other than deaths reported in the studies are summarized in Section "7.2 Adverse events reported in the clinical studies," and study results relating to PK in Section "6.1 Clinical pharmacology." Since Study TB-BC010088 had been submitted with the application for the initial approval (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013"), the summary of study is omitted from this review report.

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I study (CTD 5.3.5.2-3, Study BV-HLALCL [ongoing since [redacted], 20[redacted]; data cutoff on [redacted], 20[redacted]])

An open-label uncontrolled study was conducted at 4 sites in Japan to evaluate the safety, PK, etc. of brentuximab vedotin in patients with relapsed or refractory CD30-positive HL or sALCL aged ≥2 to <18 years (target sample size, 6 to 9 patients).

Brentuximab vedotin 1.8 mg/kg was intravenously administered every 3 weeks, and the treatment was continued until disease progression or withdrawal criteria met.

Among 6 patients enrolled, 1 had no evaluable lesions. The remaining 5 were included in efficacy analyses. All 6 enrolled patients were treated with brentuximab vedotin, and were subjected to the safety analysis set and dose limiting toxicity (DLT).

During the 21 days after the first dose of brentuximab vedotin, defined as the DLT assessment period, no DLTs were observed.

The investigator-assessed response rates according to the International Working Group (IWG) criteria (*J Clin Oncol.* 2007;25:579-86) are shown in Table 7.

Table 7. Best overall response and response rate
(Efficacy analysis set, investigator-assessed [data cutoff on [redacted], 20[redacted]])

Best overall response	HL n (%) N = 4	sALCL n (%) N = 1
CR	1 (25.0)	1 (100)
PR	1 (25.0)	0
SD	1 (25.0)	0
PD	1 (25.0)	0
Response (CR + PR) (Response rate [95% CI])	3 (60.0[14.7, 94.7])	

The investigator-assessed response rate (95% confidence interval [CI]) was 75.0% (3 of 4 patients) [19.4%, 99.4%] in patients with relapsed[9)] CD30-positive HL or sALCL, and 0% (0 of 1 patient) [0%, 97.5%] in patients with refractory[10)] CD30-positive HL.

The safety analysis revealed no deaths during the treatment period or within 30 days after the last dose.

7.1.2 Global clinical study

7.1.2.1 Global phase III study (CTD 5.3.5.1-1, Study 014 [ongoing since January 2013; data cutoff on August 15, 2018])

A double-blind, randomized, comparative study was conducted at 132 sites in 17 counties/regions including Japan to evaluate the efficacy and safety of brentuximab vedotin/CHP in patients with previously untreated CD30-positive PTCL[11)] aged ≥18 years (target sample size, 450 patients) in comparison with CHOP.

Each treatment cycle consisted of 21 days. In the brentuximab vedotin/CHP group, brentuximab vedotin 1.8 mg/kg was intravenously administered on Day 1 of each cycle in combination with CHP.[4)] In the CHOP group, patients were treated with CHOP.[3)12)] In both groups, the treatment was continued for 6 to 8 cycles unless disease progression or withdrawal criteria met.

9) Patients who experienced disease progression after achieving a CR following any prior therapy
10) Patients who failed to achieve a CR following the initial therapy
11) Patients with anaplastic lymphoma kinase (*ALK*)-positive sALCL with an international prognosis index (IPI) score <2 were ineligible for the study.
12) In Study 014, prednisone, which is unapproved in Japan, was used as a concomitant drug. The applicant, however, explained that prednisone is metabolized to prednisolone, its active metabolite, *in vivo*, and prednisolone exhibits its pharmacological effect, and that prednisone and prednisolone are therefore equivalent in terms of activity (*Goodman & Gilman's The pharmacological basis of*

All 452 patients enrolled and randomized (226 in the brentuximab vedotin/CHP group and 226 in the CHOP group) were included in the intention-to-treat (ITT) population and subjected to efficacy analyses. Of the 452 patients in the ITT population, 449 (223 in the brentuximab vedotin/CHP group and 226 in the CHOP group) were included in the safety analysis set and 3 (all in the brentuximab vedotin/CHP group) were excluded because they did not receive the study drug.

Centrally-assessed PFS according to the IWG criteria (the primary endpoint) is shown in Table 8, and the Kaplan-Meier curves of PFS in Figure 1. The results demonstrated the superiority of brentuximab vedotin/CHP in PFS over CHOP.

Table 8. Primary PFS analysis (ITT population, centrally-assessed [data cutoff on August 15, 2018])

	Brentuximab vedotin/CHP	CHOP
N	226	226
Number of events (%)	95 (42.0)	124 (54.9)
Median [95% CI](months)	48.2 [35.2, NE]	20.8 [12.7, 47.6]
Hazard ratio [95% CI]*1	0.71 [0.54, 0.93]	
P-value (2-sided)*2	0.0110	

*1 Cox proportional hazard model stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)
*2 Log-rank test stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5), with a 2-sided significance level of 0.05

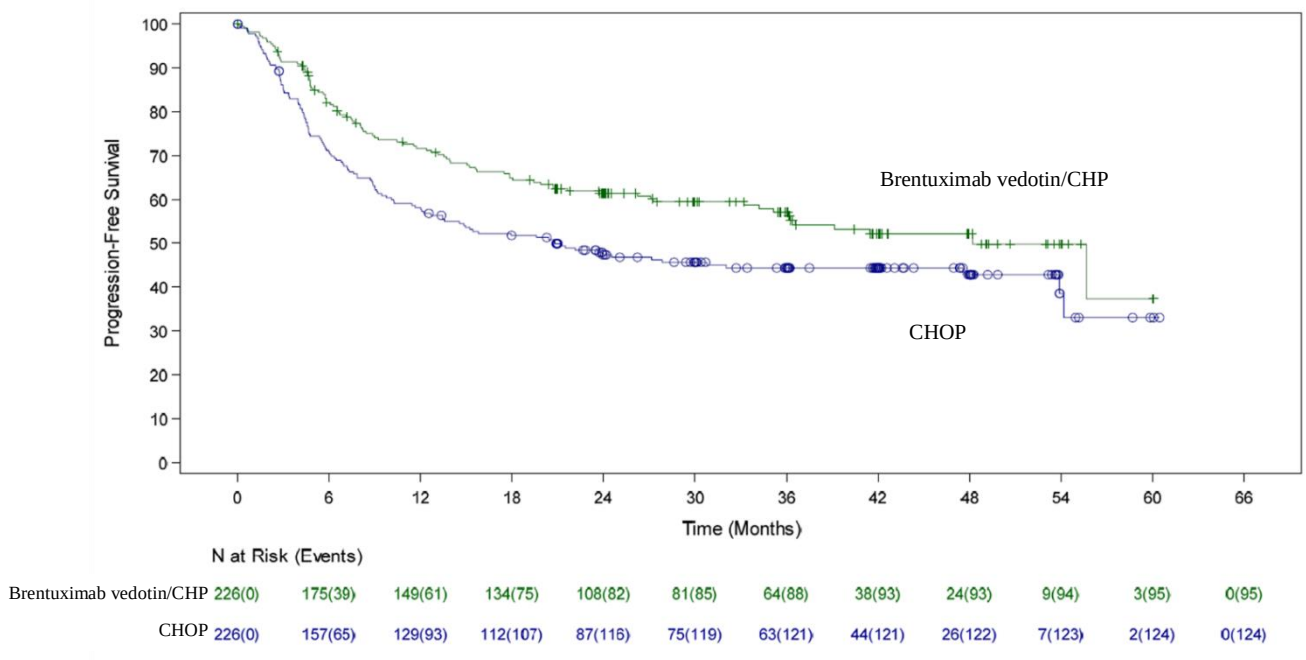

Figure 1. Kaplan-Meier curves of PFS (ITT population, centrally assessed [data cutoff on April 15, 2018])

The safety analysis revealed deaths during the treatment period or within 30 days after the last dose in 8 of 223 patients (3.6%) in the brentuximab vedotin/CHP group and 13 of 226 patients (5.8%) in the CHOP group. The

therapeutics, 11th Edition, Hirokawa Shoten Co.), and replacing prednisone with prednisolone is unlikely to affect the efficacy or safety of brentuximab vedotin administered in combination with CHP.

causes of the deaths other than disease progression in 11 patients (4 in the brentuximab vedotin/CHP group and 7 in the CHOP group) in the brentuximab vedotin/CHP group were cardiac arrest, pneumonia aspiration, pulmonary cavitation, and ventricular fibrillation in 1 patient each, while those in the CHOP group were sepsis in 2 patients, and multiple organ dysfunction syndrome, cardiac arrest, arrhythmia, and death (unknown cause) in 1 patient each. A causal relationship to the study drug could not be ruled out for the pneumonia aspiration and ventricular fibrillation in 1 patient each in the brentuximab vedotin/CHP group, and sepsis in 2 patients, multiple organ dysfunction syndrome and cardiac arrest in 1 patient each in the CHOP group.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.5.2-1, Study 011 [February 2011 to May 2017])

An open-label uncontrolled study was conducted at 10 sites outside Japan to evaluate the safety, etc. of brentuximab vedotin + CHOP sequential treatment and brentuximab vedotin/CHP combination treatment in patients with previously untreated CD30-positive PTCL[11)] aged ≥18 years (target sample size: Arm 1 [the sequential treatment group], 20 patients with sALCL; Arm 2 [the dose confirmation part for the combination treatment group], 6 to 12 patients with sALCL; Arm 3 [the extension part for the combination treatment group], 20 patients with PTCL).

The treatment cycle consisted of 21 days in all arms. In Arm 1, brentuximab vedotin 1.8 mg/kg was intravenously administered on Day 1 of Cycles 1 and 2, and CHOP was administered in Cycle 3 onward for 6 cycles. Brentuximab vedotin 1.8 mg/kg was resumed after the completion of CHOP treatment. In Arms 2 and 3, in combination with CHP, brentuximab vedotin 1.8 mg/kg was intravenously administered on Day 1 of each cycle. Patients continued to receive CHOP (Arm 1) or CHP (Arms 2 and 3) up to 6 cycles; and brentuximab vedotin alone up to 10 cycles (Arms 1, 2, and 3) unless experiencing disease progression or discontinuation criteria met.

All 39 enrolled patients (13 in Arm 1, 6 in Arm 2, and 20 in Arm 3) were treated with brentuximab vedotin and subjected to the safety analysis. Of the 39 patients, 6 in Arm 2 were subjected to DLT assessment.

Cycle 1 was the DLT assessment period, during which a DLT (Grade 3 rash pruritic) was observed in 1 of 6 patients, but the maximum tolerated dose (MTD) was not reached.

The safety analysis revealed no deaths during the treatment period or within 30 days after the last dose.

7.1.3.2 Global phase I/II study (CTD 5.3.5.2-2, Study C25002 [April 2012 to May 2018])

An open-label uncontrolled study was conducted at 12 sites outside Japan to evaluate the safety, efficacy, etc. of brentuximab vedotin in patients with relapsed or refractory HL or sALCL aged ≥2 to <18 years[5)] (target sample size: up to 12 patients for the Phase I part and 30[13)] [15 patients with HL and 15 patients with sALCL] for the Phase II part).

13) The target sample size of 30 patients included patients who were enrolled in the Phase I part and received brentuximab vedotin at the recommended dose determined in the Phase I part.

Brentuximab vedotin 1.4 or 1.8 mg/kg was intravenously administered every 3 weeks for up to 16 doses unless experiencing disease progression or discontinuation criteria met.

Among 36 enrolled patients (12 in the Phase I part and 24 in the Phase II part [excluding patients enrolled in the Phase I part]), 32 patients who received brentuximab vedotin 1.8 mg/kg (15 patients with HL and 17 patients with sALCL)[14] were subjected to the primary efficacy analysis. All 36 patients were treated with brentuximab vedotin and subjected to the safety analysis. Of these 36 patients, 12 patients enrolled in the Phase I part were subjected to DLT assessment.

During the 21-day DLT assessment period after the first dose of brentuximab vedotin in the Phase I part, 1 of 9 patients in the 1.8 mg/kg cohort experienced DLTs (Grade 3 hepatotoxicity and febrile neutropenia), but the MTD was not reached. The dosage regimen for the Phase II part was thus determined to be 1.8 mg/kg.

The centrally-assessed response rates according to the IWG criteria (the primary endpoint) in patients treated with brentuximab vedotin 1.8 mg/kg are shown by histopathological type in Table 9.

Table 9. Best overall response and response rate by histopathological type (patients receiving brentuximab vedotin 1.8 mg/kg, centrally assessed)

Best overall response	HL n (%) N = 15	sALCL n (%) N = 17
CR	5 (33.3)	7 (41.2)
PR	2 (13.3)	2 (11.8)
SD	2 (13.3)	5 (29.4)
PD	6 (40.0)	3 (17.6)
Response (CR + PR) (Response rate [95% CI])	7 (46.7 [21.3, 73.4])	9 (52.9 [27.8, 77.0])

The centrally-assessed response rates [95% CI] in patients with relapsed[15] CD30-positive HL and sALCL receiving brentuximab vedotin 1.8 mg/kg were 66.7 % (6 of 9 patients) [29.9%, 92.5%] and 54.5% (6 of 11 patients) [23.4%, 83.3%], respectively. The centrally-assessed response rates [95% CI] in patients with refractory[16] CD30-positive HL and sALCL receiving brentuximab vedotin 1.8 mg/kg were 0% (0 of 5 patients) [0%, 52.2%] and 25.0% (1 of 4 patients) [0.6%, 80.6%], respectively.

The safety analysis revealed deaths during the treatment period or within 30 days after the last dose in 1 of 36 patients (2.8%). The cause of the death was cardiac arrest (1 patient in the 1.8 mg/kg cohort of the Phase I part), for which a causal relationship to the study drug was ruled out.

7.1.3.3 Foreign phase II study (CTD 5.3.5.2-5, Study 012 [August 2011 to June 2015])

14) A patient with HL treated with brentuximab vedotin 1.8 mg/kg died before undergoing the treatment response assessment and was excluded from the primary efficacy analysis.
15) Patients who achieved PR or CR by the latest prior therapy and experienced disease progression afterward
16) Patients who did not respond to the latest prior therapy

An open-label uncontrolled study was conducted at 33 sites overseas to evaluate the efficacy, safety, etc. of brentuximab vedotin in patients with relapsed or refractory CD30-positive NHL[17] aged ≥12 (target sample size: 95 patients [30 with PTCL and 65 with B-cell lymphoma] for Part A, 15 patients with DLBCL for Part B, and 50 patients with DLBCL for Part C).

In Parts A and C, brentuximab vedotin 1.8 mg/kg was intravenously administered every 3 weeks. In Part B, brentuximab vedotin 1.8 mg/kg and rituximab (RIT) 375 mg/m^2 were intravenously administered every 3 weeks (for RIT, up to 8 doses). The treatment was continued until disease progression or withdrawal criteria met.

Among 176 patients enrolled, 172 (103 in Part A [35 patients with PTCL[18], 68 patients with B-cell lymphoma], 16 in Part B, and 53 in Part C) were treated with brentuximab vedotin. Of these 172 patients, 7 were excluded from the efficacy analysis set due to failure to undergo pre-treatment assessment or other reasons, and the remaining 165 (101 in Part A [34 patients with PTCL and 67 patients with B-cell lymphoma], 12 in Part B, and 52 in Part C) were subjected to the efficacy analyses. All 172 patients were treated with brentuximab vedotin and included in the safety analysis set.

The investigator-assessed response rates[19] (the primary endpoint) in patients with relapsed or refractory CD30-positive PTCL in Part A are shown in Table 10.

Table 10. Best overall response and response rate (patients with PTCL in Part A, investigator-assessed)

Best overall response	n (%) N = 34
CR	8 (23.5)
PR	6 (17.6)
SD	6 (17.6)
PD	14 (41.2)
Response (CR + PR) (Response rate [95% CI])	14 (41.2 [24.6, 59.3])

The investigator-assessed response rates [95% CI] were 66.7% (8 of 12 patients) [34.9%, 90.1%] in patients with relapsed[20] CD30-positive PTCL and 27.3% (6 of 22 patients) [10.7%, 50.2%] in patients with refractory[21] CD30- positive PTCL.

17) Patients with ALCL were not enrolled in the study, because Study 0004 in patients with relapsed or refractory CD30-positive sALCL had demonstrated a certain level of efficacy of brentuximab vedotin in the treatment of this patient population (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013").

18) The median age (range) of the enrolled patients was 64 (33 to 83) years.

19) The threshold response rate was set at 10% as a clinically significant response rate in the treatment of relapsed or refractory CD30-positive PTCL.

20) Patients who had received 1 regimen of prior therapy and experienced disease progression ≥3 months after achieving CR by the latest therapy, or patients who had received ≥2 regimens of prior therapy and experienced disease progression after achieving a PR or CR by the latest therapy

21) Patients who had received 1 regimen of prior therapy and failed to achieve CR by the latest therapy or experienced disease progression <3 months after achieving CR by the latest therapy, or patients who had received ≥2 regimens of prior therapy and did not respond to the latest therapy

The safety analysis revealed deaths during the treatment period or within 30 days after the last dose in 3 of 35 patients (8.6%) with relapsed or refractory CD30-positive PTCL enrolled in Part A. The cause of these deaths, other than disease progression in 2 patients, was acute respiratory distress syndrome in 1 patient, for which a causal relationship to the study drug could not be ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA selected the data to be used for the review as follows:

The global phase III study in adults with previously untreated CD30-positive PTCL (Study 014) was important for evaluating the efficacy and safety of brentuximab vedotin in the treatment of this patient population. Therefore, it was decided that the efficacy and safety evaluations of brentuximab vedotin be primarily based on the results from Study 014. Efficacy in Japanese adults with previously untreated CD30-positive PTCL was evaluated from the viewpoint of the consistency between the entire study population and the Japanese subpopulation of Study 014 according to "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 other applicable guidelines.

The foreign phase I/II study in children with relapsed or refractory HL or sALCL (Study C25002) was important for evaluating the efficacy and safety of brentuximab vedotin in this patient population. Therefore, it was decided that the efficacy and safety evaluations of brentuximab vedotin in this patient population be primarily based on the results from Study C25002. The efficacy and safety evaluations of brentuximab vedotin in Japanese children with relapsed or refractory CD30-positive HL or ALCL primarily focused on the results from the Japanese phase I study (Study BV-HLALCL).

7.R.2 Efficacy

Based on the discussion presented below, PMDA concluded that the efficacy of brentuximab vedotin administered in combination with CHP was demonstrated in patients with previously untreated CD30-positive PTCL.

PMDA also concluded that brentuximab vedotin monotherapy was demonstrated to have a certain level of efficacy in the treatment of children with relapsed or refractory CD30-positive HL or sALCL.

7.R.2.1 Efficacy of brentuximab vedotin in adult patients with CD30-positive PTCL

7.R.2.1.1 Control group in Study 014

The applicant's explanation about the rationale for the control group selected in Study 014:

When Study 014 was being planned (20[redacted]), the National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN guidelines) (v.2, 2011) and other guidelines recommended CHOP as a standard therapy for previously untreated PTCL. Therefore, CHOP was selected as a control in Study 014 involving patients with previously untreated CD30-positive PTCL.

PMDA accepted the applicant's explanation.

7.R.2.1.2 Efficacy endpoints in Study 014

The applicant's explanation about the primary efficacy endpoint of Study 014:

Patients with previously untreated CD30-positive PTCL who are not able to achieve a CR after a chemotherapy continuing for a certain period will require additional treatment. Therefore, achieving and sustaining CR is of clinical significance.

In Study 014, "disease progression," "death," and "the administration of a subsequent therapy on disease progression or residual lesions" were defined as PFS events. The prolongation of PFS based on the defined events would lead to sustained response to the therapy without having to undergo subsequent therapies, and thus is clinically significant. Accordingly, PFS based on the defined events was set as the primary endpoint of the study.

PMDA's view:

The appropriate primary endpoint of Study 014 should have been overall survival (OS), given that the treatment for patients with previously untreated PTCL aims to cure the disease. However, the applicant pointed out the clinical significance of prolonged PFS specifically defined in Study 014 for patients with previously untreated PTCL, which is understandable to some extent. Therefore, PMDA will focus primarily on the results of centrally-assessed PFS (the primary endpoint) and will check OS results as well.

7.R.2.1.3 Efficacy evaluation results in Study 014

The results of Study 014 demonstrated the superiority of brentuximab vedotin/CHP over CHOP in centrally-assessed PFS according to the IWG criteria (the primary endpoint) [see Section 7.1.2.1].

The investigator-assessed PFS according to the IWG criteria is shown in Table 11.

Table 11. PFS analysis (ITT population, investigator-assessed [data cutoff on August 15, 2018])

	Brentuximab vedotin/CHP	CHOP
N	226	226
Number of events (%)	91 (40.3)	120 (53.1)
Median [95% CI](months)	49.8 [41.5, NE]	23.8 [13.6, NE]
Hazard ratio [95% CI]*1	0.70 [0.53, 0.92]	
P-value (2-sided)*2	0.0096	

*1 Cox proportional hazard model stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)
*2 Log-rank test stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)

In Study 014, when the primary endpoint showed a statistically significant difference between the brentuximab vedotin/CHP group and the CHOP group, the secondary endpoints were assessed by a hierarchical hypothesis test in the following order: (a) centrally-assessed PFS in patients with *ALK*-positive sALCL, (b) centrally-assessed CR rate in the entire study population, (c) OS, and (d) response rate. As a result, a statistically

significant difference was identified in all these secondary endpoints between the brentuximab vedotin/CHP group and the CHOP group.

The results of the OS (a secondary endpoint) analysis are shown in Table 12, and the Kaplan-Meier curves of OS in Figure 2.

Table 12. OS analysis (ITT population [data cutoff on August 15, 2018])

	Brentuximab vedotin/CHP	CHOP
N	226	226
Number of deaths (%)	51 (22.6)	73 (32.3)
Median [95% CI](months)	NE [NE, NE]	NE [54.2, NE]
Hazard ratio [95% CI]*1	0.66 [0.46, 0.95]	
P-value (2-sided)*2	0.0244	

*1 Cox proportional hazard model stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)
*2 Log-rank test stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5), with a 2-sided significance level of 0.05

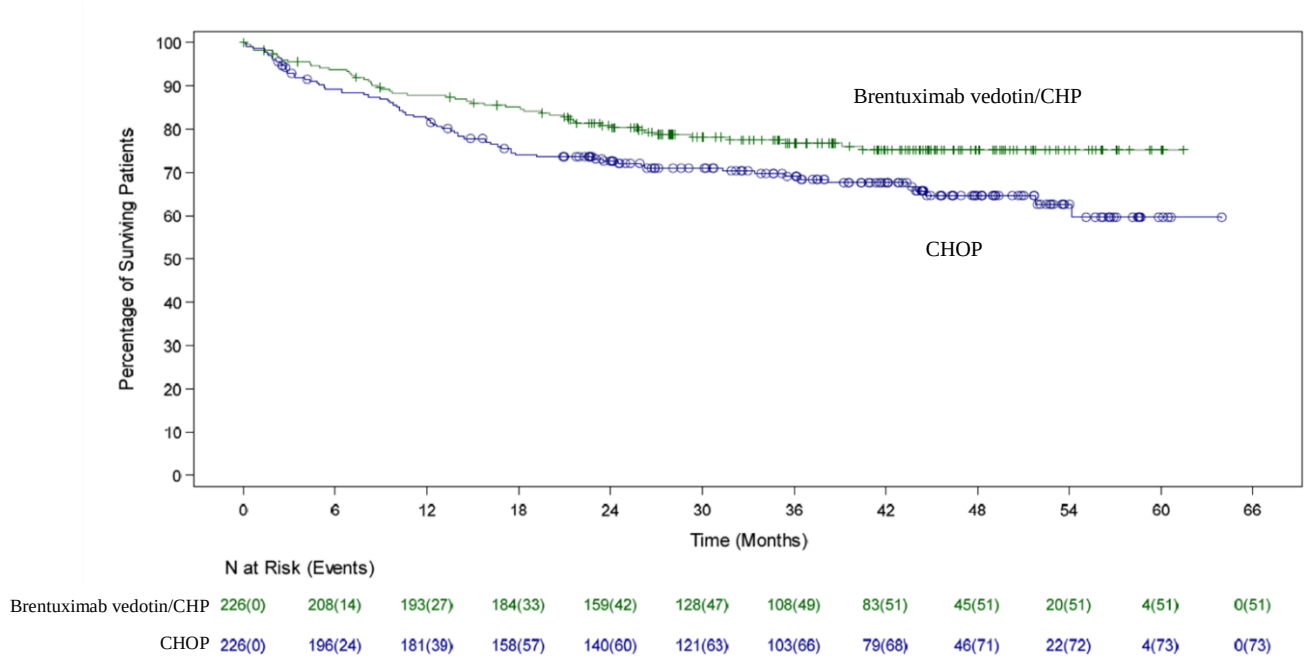

Figure 2. Kaplan-Meier curves of OS (ITT population [data cutoff on August 15, 2018])

Table 13 shows the results of the primary PFS (assessed centrally according to the IWG criteria) analysis in the Japanese subpopulation of Study 014, and Figure 3 shows the Kaplan-Meier curves of PFS.

Table 13. Primary PFS analysis in Japanese patients (ITT population, centrally assessed [data cutoff on August 15, 2018])

	Brentuximab vedotin/CHP	CHOP
N	20	23
Number of events (%)	10 (50.0)	13 (56.5)
Median [95% CI](months)	55.7 [6.28, NE]	27.1 [7.23, NE]
Hazard ratio [95% CI]*1	0.82 [0.36, 1.89]	
P-value (2-sided)*2	0.6409	

*1 Cox proportional hazard model stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)
*2 Log-rank test stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)

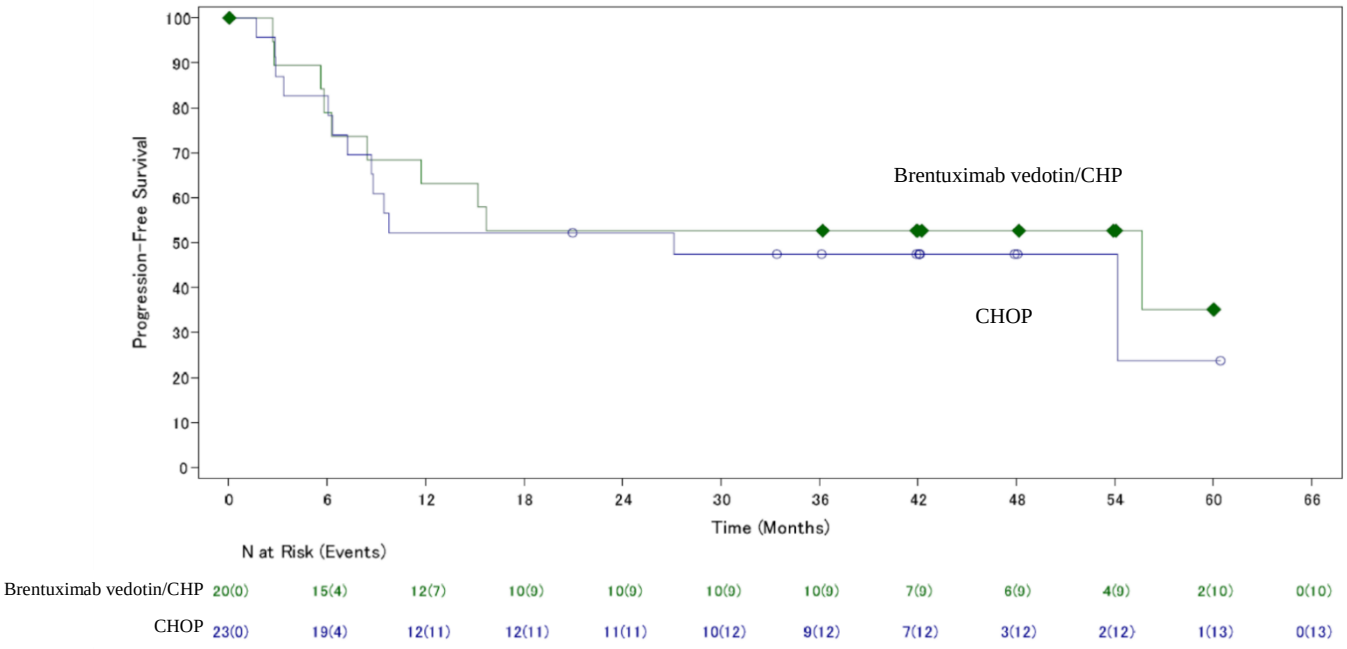

Figure 3. Kaplan-Meier curves of Primary PFS analysis in Japanese patients
(ITT population, centrally assessed [data cutoff on August 15, 2018])

Table 14 shows the results of the OS analysis in the Japanese subpopulation of Study 014, and Figure 4 shows the Kaplan-Meier curves of OS.

Table 14. OS analysis in Japanese patients (ITT population, centrally assessed [data cutoff on August 15, 2018])

	Brentuximab vedotin/CHP	CHOP
N	20	23
Number of deaths (%)	4 (20.0)	7 (30.4)
Median [95% CI](months)	NE [NE, NE]	54.2 [35.4, NE]
Hazard ratio [95% CI]*1	0.56 [0.16, 1.92]	
P-value (2-sided)*2	0.3472	

*1 Cox proportional hazard model stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)
*2 Log-rank test stratified by *ALK* fusion genes (with vs. without) and IPI score (0 to 1, 2 to 3, vs. 4 to 5)

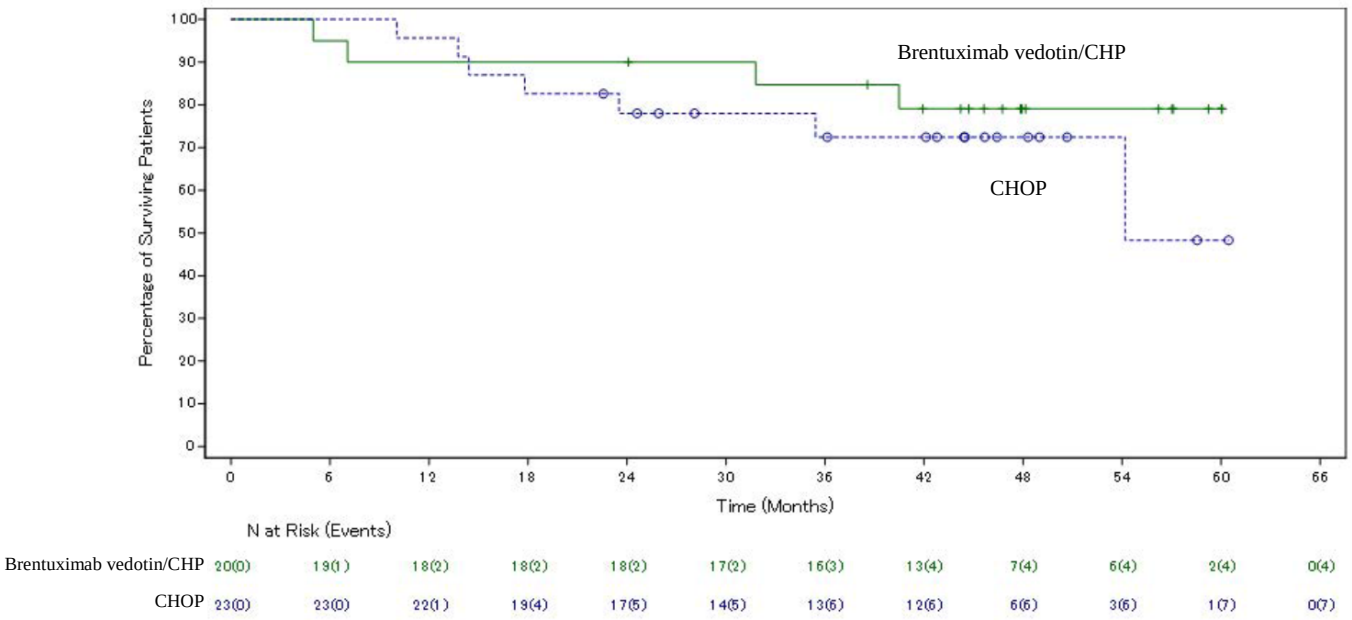

Figure 5. Kaplan-Meier curves of OS in Japanese patients (ITT population [data cutoff on August 15, 2018])

PMDA's view:

PMDA concluded that brentuximab vedotin/CHP was shown to be effective in adults with previously untreated CD30-positive PTCL in view of the following observations, etc.

- The results of Study 014 demonstrated the superiority of brentuximab vedotin/CHP over CHOP in the primary endpoint of PFS assessed according to the IWG criteria.

- The results of Study 014 showed a statistically significant prolongation of OS by brentuximab vedotin/CHP as compared with CHOP.

- Although the small number of Japanese participants in Study 014 precluded a precise evaluation, the results of PFS and OS in the Japanese subpopulation did not tend to clearly differ from those in the entire study population.

7.R.2.2 Efficacy in pediatric patients with relapsed or refractory CD30-positive HL or sALCL

The applicant's explanation about the efficacy of brentuximab vedotin in children with relapsed or refractory CD30-positive HL or sALCL:

The results of Study C25002 in patients with relapsed or refractory HL or sALCL aged ≥2 to <18 years[5)] showed a certain level of response to brentuximab vedotin 1.8 mg/kg [see Section 7.1.3.2]. In addition, in Phase II part of the study, the centrally-assessed response rate [95% CI] according to the IWG criteria was 45.8% (11 of 24 patients) [25.6%, 67.2%］(33.3% [3 of 9 patients] [7.5%, 70.1%] in children with HL and 53.3% [8 of 15 patients] [26.6%, 78.7%] in children with sALCL).

Although the extremely small number of Japanese participants in Study BV-HLALCL precluded a precise evaluation of the efficacy of brentuximab vedotin in Japanese children with relapsed or refractory CD30-positive HL or sALCL, the investigator-assessed response rate according to the IWG criteria in the Japanese pediatric subpopulation of the study was 60.0% (3 of 5 patients) [14.7%, 94.7%] (50.0% [2 of 4 patients] in patients with HL and 100% (1 of 1 patient) in the patients with sALCL) [see Section 7.1.1.1].

The following observations as well as the above results indicate that brentuximab vedotin was demonstrated to have a certain level of efficacy in the treatment of children with relapsed or refractory CD30-positive HL or sALCL.

- The response rates with brentuximab vedotin administered alone in children with relapsed or refractory CD30-positive HL or sALCL (Phase II Part of Study C25002) did not differ markedly from those in adults with relapsed or refractory CD30-positive HL (Study 0003) or sALCL (Study 0004) (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013") [see Section 7.1.3.2].

- There are no clear differences in the diagnostic or treatment system for relapsed or refractory CD30-positive HL or sALCL between children and adults.

- There have been no clear differences in the PK of brentuximab vedotin between children and adults [see Section 6.R.1].

PMDA accepted the applicant's explanation.

7.R.3 Safety

According to the discussions in the subsections below, PMDA concluded as follows:
Brentuximab vedotin therapy for adults with CD30-positive PTCL and children with relapsed or refractory CD30-positive HL or ALCL requires particular attention to adverse events, i.e., infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome, lung disorders, acute pancreatitis, and hepatic dysfunction. These are the known adverse events of brentuximab vedotin warranting attention, which were identified during the previous reviews for the approved indications (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013" and "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated August 3, 2018). Continued attention is required to these events in the use of brentuximab vedotin, as practiced in its use for the approved indications.

Although caution should be used against the above-mentioned adverse events, brentuximab vedotin is tolerable in adults with CD30-positive PTCL and child with relapsed or refractory CD30-positive HL or ALCL, given appropriate measures, i.e., monitoring and management of adverse events, dose delay or reduction, treatment

discontinuation, taken by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.1 Safety of brentuximab vedotin in adult patients with CD30-positive PTCL

7.R.3.1.1 Safety profile of brentuximab vedotin in adult patients with CD30-positive PTCL

The applicant's explanation about the safety profile of brentuximab vedotin in adults:

Table 15 presents a summary of the safety data from Study 014. In Study 014, adverse events leading to dose interruption were not collected.

Table 15. Safety summary (Study 014)

	n (%)	
	Brentuximab vedotin/CHP N = 223	CHOP N = 226
All adverse events	221 (99.1)	221 (97.8)
Grade ≥ 3 adverse events	147 (65.9)	146 (64.6)
Adverse events resulting in death	8 (3.6)	16 (7.1)
Serious adverse events	87 (39.0)	87 (38.5)
Adverse events leading to discontinuation of study drug*	16 (7.2)	19 (8.4)
Adverse events leading to discontinuation of brentuximab vedotin	4 (1.8)	-
Adverse events leading to dose reduction of study drug*	37 (16.6)	30 (13.3)
Adverse events leading to dose reduction of brentuximab vedotin	21 (9.4)	-

* ≥1 of the following drugs: brentuximab vedotin, cyclophosphamide, doxorubicin, vincristine, or prednisone (unapproved in Japan)

In Study 014, the adverse event of any grade reported with a ≥10% higher incidence in the brentuximab vedotin/CHP group than in the CHOP group was diarrhoea (38.1% [85patients] in the brentuximab vedotin group, 20.4% [46 patients] in the CHOP group). The serious adverse events reported with a ≥2% higher incidence in the brentuximab vedotin/CHP group than in the CHOP group were pneumonia (4.9% [11 of 223 patients], 1.3% [3 patients]), febrile neutropenia (13.9% [31 patients], 11.5% [26 patients]), and pneumonitis (2.2% [5 patients], 0%). The adverse event leading to dose reduction of the study drug with a ≥3% higher incidence in the brentuximab vedotin/CHP group than in the CHOP group was peripheral sensory neuropathy (4.9% [11 patients], 1.8% [4 patients]). In the brentuximab vedotin/CHP group, there were no Grade ≥3 adverse events with a ≥5% higher incidence, adverse events leading to the discontinuation of study drug with a ≥3% higher incidence, or adverse events resulting in death with a ≥1% higher incidence than in the CHOP group.

The applicant's explanation about differences in the safety profile of brentuximab vedotin between patients with relapsed or refractory CD30-positive ALCL (the approved indication) and patients with previously untreated CD30-positive PTCL:

Table 16 presents a summary of the safety data from patients with previously untreated CD30-positive PTCL in the brentuximab vedotin/CHP group of Study 014 and patients with relapsed or recurrent CD30-positive sALCL in Study 0004.

Table 16. Safety summary in the brentuximab vedotin/CHP group of Study 014 and Study 0004

	n (%)	
	Study 014 Brentuximab vedotin/CHP N = 223	Study 0004 (Brentuximab vedotin alone) N = 58
All adverse events	221 (99.1)	58 (100)
Grade ≥3 adverse events	147 (65.9)	36 (62.1)
Adverse events resulting in death	8 (3.6)	6 (10.3)
Serious adverse events	87 (39.0)	25 (43.1)
Adverse events leading to discontinuation of brentuximab vedotin	4 (1.8)	16 (27.6)
Adverse events leading to dose reduction of brentuximab vedotin	21 (9.4)	7 (12.1)

The adverse events of any grade reported with a 10% higher incidence in the brentuximab vedotin/CHP group of Study 014 than in Study 0004 were febrile neutropenia (18.4% [41patients] in Study 014, 0% in Study 0004), neutropenia (38.1% [85 patients], 20.7% [12 patients]), alopecia (26.0% [58 patients], 13.8% [8 patients]), and anaemia (20.6% [46 patients], 10.3% [6 patients]). The Grade ≥3 adverse events reported with a ≥5% higher incidence in the brentuximab vedotin/CHP group of Study 014 than in Study 0004 were febrile neutropenia (18.4% [41 patients], 0%), neutropenia (34.5% [77 patients], 20.7% [12 patients]), anaemia (13.5% [30 patients], 6.9% [4 patients]), and leukopenia (7.2% [16 patients], 1.7% [1 patients]). The serious adverse event reported with a ≥5% higher incidence in the brentuximab vedotin/CHP group of Study 014 than in Study 0004 was febrile neutropenia (13.9% [31 patients], 0%). There were no adverse events resulting in death or leading to discontinuation or dose reduction of brentuximab vedotin, with a ≥2% higher incidence in the brentuximab vedotin/CHP group of Study 014 than in Study 0004.

The available results from the all-case post-marketing surveillance on brentuximab vedotin for the approved indication of relapsed or refractory CD30-positive HL or ALCL identified no events that warrant additional cautionary advice.

In addition, patients with PTCL in Part A of Study 012 experienced no adverse events of any grade with a ≥20% higher incidence, Grade ≥3 adverse events, adverse events resulting in death, serious adverse events, or adverse events leading to the discontinuation or dose reduction of brentuximab vedotin with a ≥10% higher incidence than in Study 0004.

PMDA's view:

The use of brentuximab vedotin for patients with previously untreated CD30-positive PTCL requires attention to the adverse events that were more frequently reported in the brentuximab vedotin/CHP group than in the CHOP group in Study 014. However, considering that these adverse events are all known events of brentuximab vedotin and the concomitant CHP, brentuximab vedotin/CHP is tolerable in adults with CD30-positive PTCL, given appropriate measures, i.e., monitoring and management of adverse events, taken by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.1.2 Differences in safety between Japanese and non-Japanese adult patients with CD30-positive PTCL

The applicant's explanation about differences in the safety of brentuximab vedotin between Japanese and non-Japanese adult patients based on the safety data from Study 014:

Table 17 presents a summary of the safety data from Japanese and non-Japanese patients in Study 014.

Table 17. Safety summary in Japanese and non-Japanese patients (Study 014)

	n (%)			
	Japanese		Non-Japanese	
	Brentuximab vedotin/CHP N = 20	CHOP N = 23	Brentuximab vedotin/CHP N = 203	CHOP N = 203
All adverse events	20 (100)	23 (100)	201 (99.0)	198 (97.5)
Grade ≥3 adverse events	20 (100)	23 (100)	127 (62.6)	123 (60.6)
Adverse events resulting in death	0	0	8 (3.9)	13 (6.4)
Serious adverse events	5 (25.0)	8 (34.8)	82 (40.4)	79 (38.9)
Adverse events leading to discontinuation of the study drug*	1 (5.0)	1 (4.3)	15 (7.4)	18 (8.9)
Adverse events leading to discontinuation of brentuximab vedotin	0	-	4 (2.0)	-
Adverse events leading to dose reduction of the study drug*	7 (35.0)	5 (21.7)	30 (14.8)	25 (12.3)
Adverse events leading to dose reduction of brentuximab vedotin	2 (10.0)	-	19 (19.4)	-

* ≥1 of the following drugs: brentuximab vedotin, cyclophosphamide, doxorubicin, vincristine, or prednisone (unapproved in Japan)

In the brentuximab vedotin/CHP group of Study 014, the adverse events of any grade occurring at a ≥30% higher incidence in Japanese patients than in non-Japanese patients were alopecia (80.0% [16 patients] in Japanese patients, 20.7% [42 patients] in non-Japanese patients), neutropenia (85.0% [17patients], 33.5% [68 patients]), nausea (80.0% [16 patients], 42.9% [87 patients]), constipation (65.0% [13 patients], 25.1% [51 patients]), decreased appetite (50.0% [10 patients], 14.3% [29 patients]), febrile neutropenia (50.0% [10 patients], 15.3% [31 patients]), and stomatitis (40.0% [8 patients], 9.4% [19 patients]). The Grade ≥3 adverse events with a ≥10% higher incidence in Japanese patients than in non-Japanese patients were neutropenia (85.0% [17 patients], 29.6% [60 patients]), febrile neutropenia (50.0% [10 patients], 15.3% [31 patients]), leukopenia (25.0% [5 patients], 5.4% [11 patients]), and diarrhoea (15.0% [3 patients], 4.9% [10 patients]). The adverse events leading to dose reduction of the study drug with a ≥10% higher in Japanese patients than in non-Japanese patients were febrile neutropenia (15.0% [3patients], 1.5% [3 patients]) and neutropenia (15.0% [3 patients], 2.0% [4 patients]). There were no serious adverse events or adverse events resulting in death or leading to discontinuation of the study drug with a 10% higher incidence in Japanese patients than in non-Japanese patients.

In terms of hematological toxicities such as neutropenia, Japanese patients underwent testing more frequently than non-Japanese patients, which may have contributed to the differences in the incidences between Japanese and non-Japanese patients.

PMDA's view:

The small number of Japanese participants in Study 014 precludes a clear conclusion on the differences in the safety of brentuximab vedotin/CHP between Japanese and non-Japanese patients based on the results of the study. However, caution should be used against the adverse events that were more frequently reported in Japanese patients than in non-Japanese patients. Nevertheless, they are all known adverse events of brentuximab vedotin, and thus brentuximab vedotin/CHP is tolerable in Japanese adults, given appropriate measures, i.e., monitoring and management of adverse events, taken by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

The following subsection is PMDA's review on febrile neutropenia, which was more frequently reported serious adverse event in the brentuximab vedotin/CHP group of Study 014 than in the CHOP group of Study 014 or Study 0004.

7.R.3.1.3 Febrile neutropenia

The applicant's explanation about the incidence of febrile neutropenia associated with brentuximab vedotin/CHP therapy and actions taken for the event:

Febrile neutropenia-related adverse events were retrieved based on the preferred term (PT) of "febrile neutropenia" in the Medical Dictionary for Regulatory Activities (MedDRA).

In Study 014, febrile neutropenia was reported in 41 patients (18.4%) in the brentuximab vedotin/CHP group and 33 patients (14.6%) in the CHOP group. Of these patients, 5 (2.2%) in the brentuximab vedotin/CHP group and 7 (3.1%) in the CHOP group experienced Grade ≥4 febrile neutropenia.

In Study 014, a safety review was performed when the number of patients enrolled reached 293. The result revealed a high incidence of infections in the entire study population. The Independent Data Monitoring Committee advised the use of prophylaxis with granulocyte colony-stimulating factor (G-CSF) according to the American Society of Clinical Oncology (ASCO) guidelines.

Table 18 shows the incidence of febrile neutropenia, with or without G-CSF prophylaxis.

Table 18. Incidence of febrile neutropenic with or without G-CSF prophylaxis (Study 014)

MedDRA PT (MedDRA/J ver.21.0)	n (%)			
	Brentuximab vedotin/CHP		CHOP	
	Without G-CSF	With G-CSF	Without G-CSF	With G-CSF
	N = 148	N = 75	N = 165	N = 61
Febrile neutropenia	29 (19.6)	12 (16.0)	26 (15.8)	7 (11.5)

In the brentuximab vedotin/CHP group of Study 014, no patients died of febrile neutropenia. Serious febrile neutropenia was reported in 21 patients (14.2%) without G-CFS prophylaxis and 10 patients (13.3%) with G-CFS prophylaxis. A causal relationship to the study drug could not be ruled out in 17 patients (11.5%) without

G-CFS prophylaxis and 8 patients (10.7%) with G-CFS prophylaxis. No patients experienced the discontinuation or dose reduction of study drug due to febrile neutropenia.

The clinical guidelines published in and outside Japan recommend that G-CSF prophylaxis be used in a chemotherapy that presumably causes febrile neutropenia at an incidence of ≥20% *(Clinical Practice Guidelines for the Use of G-CSF Edited by the Japanese Society of Clinical Oncology 2013*. Kanehara Shuppan, 2013, Japan; and *J Clin Oncol*. 2015;33:3199-212).

In Study 014, (a) the incidence of febrile neutropenia was approximately 20% in patients who did not receive G-CFS prophylaxis in the brentuximab vedotin/CHP group, and (b) 2 patients who did not receive G-CSF prophylaxis died of infections (sepsis and pneumonia in 1 patient each), while no patients with G-CSF died of infections. Given these outcomes, the prophylactic use of G-CSF is recommended with brentuximab vedotin/CHP therapy according to the above-mentioned clinical guidelines:

PMDA's view:
In view of serious febrile neutropenia occurring more frequently following brentuximab vedotin/CHP than following CHOP or brentuximab vedotin monotherapy [see Section 7.R.3.1.1], etc., the applicant should communicate the occurrence of febrile neutropenia in patients on brentuximab vedotin/CHP in Study 014 through the package insert, etc. and, as practiced for the brentuximab vedotin/AVD therapy for the approved indication of previously untreated CD30-positive HL, should appropriately advise healthcare professionals to consider the use of G-CSF, including its prophylactic use, in the brentuximab vedotin/CHP therapy for previously untreated CD30-positive PTCL, with reference to the latest clinical practice guideline.

7.R.3.2 Safety of brentuximab vedotin in pediatric patients with relapsed or refractory CD30-positive HL and sALCL

The applicant's explanation about the safety of brentuximab vedotin in children with relapsed or refractory CD30-positive HL or sALCL based on the safety data from Studies C25002 and BV-HLALCL involving this patient population:
In both the studies, adverse events leading to dose delay were not collected.

(a) Safety profile
Table 19 presents a summary of the safety data from Studies C25002 and BV-HLALCL.

Table 19. Safety summary (the brentuximab vedotin 1.8 mg group of Study C25002, and Study BV-HLALCL)

	n (%)	
	Study C25002 brentuximab vedotin 1.8 mg/kg Non-Japanese	Study BV-HLALCL Japanese
	N = 33	N = 6
All adverse events	33 (100)	6 (100)
Grade ≥3 adverse events	16 (48.5)	3 (50.0)
Adverse events resulting in death	1 (3.0)	0
Serious adverse events	8 (24.2)	0
Adverse events leading to treatment discontinuation	2 (6.1)	0
Adverse events leading to dose reduction	3 (9.1)	1 (16.7)

In the 1.8 mg/kg group of Study C25002, the adverse events of any grade reported with a ≥15% incidence were pyrexia in 15 patients (45.5%), nausea in 11 patients (33.3%), rhinitis in 7 patients (21.2%), paraesthesia, vomiting, and pharyngitis in 6 patients (18.2%) each, and diarrhoea, neutropenia, and myalgia in 5 patients (15.2%) each. The Grade ≥3 adverse events reported by ≥2 patients were neutropenia in 4 patients (12.1%), and pyrexia and gamma-glutamyltransferase increased in 2 patients (6.1%) each. The serious adverse event reported by ≥2 patients was pyrexia in 2 patients (6.1%). There were no adverse events resulting in death or leading to treatment discontinuation or dose reduction in ≥2 patients.

In Study BV-HLALCL, adverse events reported by ≥3 patients were white blood cell count decreased and pyrexia in 5 patients (83.3%) each as well as neutrophil count decreased and upper respiratory tract infection in 3 patients (50.0%) each. The Grade ≥3 adverse events were white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased in 2 patients (33.3%) each, and anaemia 1 patient (16.7%). The adverse events leading to dose reduction were neutrophil count decreased and white blood cell count decreased in 1 patient (16.7%) each.

(b) Differences in safety profiles between Japanese and non-Japanese pediatric patients

The adverse events reported with a ≥40% higher incidence in Study BV-HLALCL than in the 1.8 mg/kg group of Study C25002 were white blood cell count decreased (83.3% [5 patients] in Study BV-HLALCL, 3.0% [1 patient] in Study C25002), upper respiratory tract infection (50.0% [3 patients], 0%), and neutrophil count decreased (50.0% [3 patients], 6.1% [2 patients]). There were no Grade ≥3 adverse events or serious adverse events reported, with a 40% higher incidence in Study BV-HLALCL than in the 1.8 mg/kg group of Study C25002. There were no adverse events resulting in death or leading to treatment discontinuation or dose reduction, with a ≥40% higher incidence in Study BV-HLALCL than in the 1.8 mg/kg group of Study C25002.

(c) Safety by age group

The adverse events of any grade reported with a ≥20% higher incidence in children with HL (receiving brentuximab vedotin 1.8 mg/kg in Study C25002) than in adults with HL (Study 0003) were pyrexia (50.0% [8 patients] in Study C25002, 29.4% [30 patients] in Study 0003) and paraesthesia (31.3% [5 patients], 3.9% [4 patients]). The Grade ≥3 adverse event reported with a ≥10% higher incidence in children with HL (receiving

brentuximab vedotin 1.8 mg/kg in Study C25002) than in adults with HL (Study 0003) was gamma-glutamyltransferase increased (12.5% [2 patients], 0%). There were no serious adverse events, adverse events resulting in death, or adverse events leading to treatment discontinuation or dose reduction, with a ≥10% higher incidence in children with HL (receiving brentuximab vedotin 1.8 mg/kg in Study C25002) than in adults with HL (Study 0003).

The adverse event reported with a ≥20% higher incidence in children with sALCL (receiving brentuximab vedotin 1.8 mg/kg in Study C25002) than in adults with sALCL (Study 0004) was rhinitis (23.5% [4 patients] in Study C25002, 3.4% [2 patients] in Study 0004). No Grade ≥3 adverse events or serious adverse events were reported. There were no adverse events resulting in death, or those leading to treatment discontinuation or dose reduction, with a ≥10% higher incidence in children with sALCL (receiving brentuximab vedotin 1.8 mg/kg in Study C25002) than in adults with sALCL (Study 0004).

The children in the 1.8 mg/kg group of Study C25002 were divided into 2 age groups of <12 years (12 patients) and ≥12 years (21 patients). All patients experienced adverse events. Adverse events for which a causal relationship to the study drug could not be ruled out were occurred in 9 patients (75.0%) aged <12 years and 14 patients (66.7%) aged ≥12 years. Adverse events with a ≥15% gap in incidence between the age groups of <12 years and ≥12 years were paraesthesia (8.3% [1 patients], 23.8% [5 patients]), headache (25.0% [3 patients], 0%), lymphocyte count decreased (16.7% [2 patients], 0%), and neutrophil count decreased (16.7% [2 patients], 0%). Grade ≥3 adverse events occurred in 41.7% (5 patients) of patients aged <12 years and 52.4% (11 patients) of patients aged ≥12 years. A causal relationship to the study drug could not be ruled out for Grade ≥3 adverse events in 3 patients (25.0%) and 6 patients (28.6%), respectively. There were no Grade ≥3 adverse events or Grade ≥3 adverse events for which a causal relationship to the study drug could not be ruled out showing a ≥15% gap in incidence between the age groups.

PMDA's view:
Although the small number of pediatric patients evaluated precludes a clear conclusion on the safety of brentuximab vedotin in children with relapsed or refractory CD30-positive HL or sALCL based on the results of clinical studies, the adverse events that were more frequently reported in children than in adults warrant attention. However, (a) those are all known adverse events of brentuximab vedotin in adults, and (b) there were no clear differences between children and adults in reported serious adverse events, etc. Brentuximab vedotin monotherapy thus is tolerable in Japanese children, given appropriate measures, i.e., monitoring and management of adverse events, taken by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.4 Clinical positioning and indication

For the present partial change application, the description of previously approved indications, "The following CD30-positive diseases: Hodgkin's lymphoma, Relapsed or refractory anaplastic large-cell lymphoma" was planned to be modified to "The following CD30-positive diseases: Hodgkin's lymphoma, Peripheral T-cell

lymphomas." The description of the "Precautions Concerning Indications" section for the approved indications was to remain unchanged as follows.

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety," and the subsections below, PMDA concluded that the "Indications" and "Precautions Concerning Indications" sections proposed by the applicant were appropriate.

7.R.4.1 Clinical positioning, intended patient population, and indications

In major clinical practice guidelines and textbooks for hematology and clinical oncology available in and outside Japan contain descriptions about brentuximab vedotin therapy for adult PTCL, and relapsed or refractory pediatric HL and PTCL as follows:

Clinical practice guidelines

- NCCN guidelines (v.2, 2019):
  - Brentuximab vedotin in combination with CHP is recommended for the treatment of patients with previously untreated PTCL (Category 1,[22)] patients with ALCL; Category 2A,[23)] patients with PTCL other than ALCL).
  - Brentuximab vedotin monotherapy is recommended for the treatment of patients with relapsed or refractory CD30-positive PTCL (Category 2A).
- ESMO guidelines (*Ann Oncol*. 2015;26 Suppl 5:v108-15):
  Brentuximab vedotin monotherapy is recommended for the treatment of patients with relapsed or refractory CD30-positive ALCL (Evidence level III, A[24)])
- A Practical Guideline for Pediatric Leukemia and Lymphoma 2016:
  Cases of patients including children with relapsed or refractory ALCL responded to brentuximab vedotin monotherapy are reported.

Text books

- Williams Hematology, Ninth edition (The McGraw-Hill Companies, Inc, 2016, USA):
  Brentuximab vedotin monotherapy is a treatment option for patients with relapsed or refractory ALCL. Brentuximab vedotin monotherapy also has promising efficacy in the treatment of patients with relapsed or refractory CD30-positive PTCL other than ALCL.

22) Based on high-level evidence, there is a uniform NCCN consensus that the intervention is appropriate.
23) Based on lower-level evidence, there is a uniform NCCN consensus that the intervention is appropriate.
24) Based on strong evidence of efficacy obtained from prospective cohort studies, the therapy has been demonstrated to have a substantial clinical benefit and is strongly recommended.

- Principles and Practice of Pediatric Oncology, Seventh edition (Lippincott Williams & Wilkins, 2016, USA):
  Brentuximab vedotin monotherapy is reported to have high efficacy in the treatment of pediatric patients with relapsed or refractory HL.

The applicant's explanation about the clinical positioning, target population, and indications of brentuximab vedotin in the treatment of (a) adults with CD30-positive PTCL and (b) children with relapsed or refractory CD30-positive HL and PTCL:

(a) Adult patients with CD30-positive PTCL:
Based on the results of Study 014 in adults with previously untreated CD30-positive PTCL, which demonstrated the clinical benefit of brentuximab vedotin in combination with CHP [see Sections 7.R.2 and 7.R.3], brentuximab vedotin/CHP will deserve recognition as a standard therapy for adults with previously untreated CD30-positive PTCL.

Adults with previously untreated CD30-positive PTCL in Part A of Study 012 showed the investigator-assessed response rate [95% CI] according to the IWG criteria of 41.2% (14 of 34 patients) [24.6%, 59.3%], which was significantly higher than the prespecified threshold response rate [see Section 7.1.3.3]. In Study 012, no Japanese patients were enrolled. However, brentuximab vedotin monotherapy has promising efficacy in Japanese adults with relapsed or refractory CD30-positive PTCL in view of the following observations.

- There are no clear differences between Japan and foreign countries in the diagnosis and treatment systems for CD30-positive PTCL.
- In Study 014 in adults with previously untreated CD30-positive PTCL, the PFS and OS in the Japanese subpopulation did not clearly differ from those in the entire study population [see Section 7.R.2.1.3].
- In the treatment for the approved indication, "relapsed or refractory ALCL," no clear differences were identified in the efficacy or safety of brentuximab vedotin between Japanese and non-Japanese patients (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013").

Approved drugs for the treatment of relapsed or refractory PTCL in adults include forodesine, hydrochloride, pralatrexate, and romidepsin. Because of no available clinical study efficacy or safety data of brentuximab vedotin compared with the approved oncology drugs, the choice of medication is presumed to be made on a patient-by-patient basis according to their condition, in light of the action mechanism, etc. of each drug.

(b) Pediatric patients with relapsed or refractory CD30-positive HL or PTCL:
Both Phase II part of Study C25002 and Study BV-HLALCL demonstrated the clinical benefit of brentuximab vedotin monotherapy in children with relapsed or refractory CD30-positive HL or sALCL [see Sections 7.R.2 and 7.R.3]. Brentuximab vedotin monotherapy thus will deserve recognition as a standard therapy for this patient population. Furthermore, brentuximab vedotin monotherapy has promising clinical benefit in children

with relapsed or refractory CD30-positive PTCL of various histopathological types other than sALCL as well [see Section 7.R.4.2].

Accordingly, the package insert of brentuximab vedotin will present the proposed indication, "The following CD30-positive diseases: Hodgkin's lymphoma, peripheral T-cell lymphoma," along with the histopathological types, etc. of patients enrolled in the clinical studies elaborated in the "CLINICAL STUDIES" section and the following cautionary advice, which remains unchanged from those for the approved indications, in the "Precautions Concerning Indications" section.

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

PMDA's view:

The results of Study 014 demonstrated that brentuximab vedotin/CHP not only prolonged PFS but also statistically significantly prolonged OS as compared with CHOP. In view of these results, brentuximab vedotin/CHP will deserve recognition as a standard therapy for adults with previously untreated CD30-positive PTCL. However, in terms of ATLL, a histopathological type of PTCL, it remains inconclusive whether brentuximab vedotin/CHP is a recommendable treatment option based on the submitted clinical study results in view of the current situation where, (a) in Japan, mLSG15 therapy[25)] is recommended as the standard therapy for previously untreated ATLL, and (b) the use of the criteria internationally agreed in 2009 (*J Clin Oncol*. 2008;27:453-9) is recommended for the efficacy evaluation for ATLL, separately from other types of PTCL (NCCN guidelines v.2, 2011).[26)]

For the treatment of adults with relapsed or refractory CD30-positive PTCL, the clinical benefit of brentuximab vedotin has not been demonstrated by controlled comparative studies. Furthermore, there are no clinical study data evaluating the efficacy of brentuximab vedotin in Japanese adults with relapsed or refractory CD30-positive PTCL. However, the following observations are indicative of a certain extent of clinical benefit of brentuximab vedotin monotherapy in this patient population. The internationally recognized textbooks and clinical guidelines also recommend brentuximab monotherapy as a treatment option for this patient population, supporting the prospect that brentuximab vedotin monotherapy be a treatment option for Japanese adults with relapsed or refractory CD30-positive PTCL.

25) Each 28-day mLSG15 cycle is composed of intravenous or oral doses of vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP) administered on Day 1, doxorubicin, ranimustine, and prednisolone (AMP) administered on Day 8, and vindesine, etoposide, carboplatin, and prednisolone (VECP) administered on Days 15 to 17, along with intrathecal doses of cytarabine, methotrexate, and prednisolone administered before starting VCAP therapy in even-numbered cycles.

26) Because ATLL is a complex disease type manifesting the pathologies of both leukemia and lymphoma, the response criteria include a variety of lesions, including peripheral blood lesions, to be assessed.

- The clinical benefit of brentuximab vedotin/CHP was demonstrated in adults with previously untreated CD30-positive PTCL, and the efficacy and safety of brentuximab vedotin do not clearly differ between Japanese and non-Japanese patients [see Sections 7.R.2 and 7.R.3].
- The results of Studies 0004 and TB-BC010088 in adults with relapsed or refractory sALCL (the approved indication) demonstrated the clinical benefit of brentuximab vedotin monotherapy, and showed no clear differences in the efficacy, safety, or PK of brentuximab vedotin between Japanese and non-Japanese patients (see "Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013").
- In adults with relapsed or refractory CD30-positive PTCL enrolled in Part A of Study 012, brentuximab vedotin monotherapy had a certain level of efficacy and was tolerable.
- Relapsed or refractory PTCL leads to a poor prognosis, and there is no established standard treatment for patients affected.

PMDA accepted the applicant's explanation about children with relapsed or refractory CD30-positive HL and PTCL.

Based on the above discussions, and given that brentuximab vedotin is presumed to be prescribed by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies, the proposed indication, "the following CD30-positive diseases: Hodgkin's lymphoma, Peripheral T-cell lymphoma" is appropriate, as long as histopathological types of the patients enrolled in the clinical studies are elaborated in the "CLINICAL STUDIES" section of the package insert, along with the cautionary advice, which remains unchanged from that for the approved indications, presented in the "Precautions Concerning Indication" section.

7.R.4.2 Histopathological types of CD30-positive PTCL

The applicant's explanation about the efficacy and safety of brentuximab vedotin, by PTCL histopathological type:

PTCL has various histopathological types, such as ATLL, angioimmunoblastic T-cell lymphoma (AITL), PTCL, not otherwise specified (PTCL-NOS), etc. in addition to ALCL, the approved indication of brentuximab vedotin (*Blood.* 2016;127:2375-90).

Study 014 in adults with previously untreated CD30-positive PTCL enrolled patients with sALCL, PTCL-NOS, AITL, ATLL, enteropathy-associated T-cell lymphoma, and hepatosplenic T-cell lymphoma. Table 20 shows the results of centrally-assessed PFS according to the IWG criteria by histopathological type in the study.

Table 20. PFS analysis by PTCL histopathological type in Study 014
(ITT population, centrally assessed [data cutoff on August 15, 2018])

PTCL histopathological type*	Treatment	N	Number of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI]
ALK-positive sALCL	Brentuximab vedotin/CHP	49	5 (10.2)	NE [NE, NE]	0.29
	CHOP	49	16 (32.7)	NE [NE, NE]	[0.11, 0.79]
ALK-negative sALCL	Brentuximab vedotin/CHP	113	50 (44.2)	48.2 [23.7, NE]	0.65
	CHOP	105	60 (57.1)	15.4 [9.03, NE]	[0.44, 0.95]
PTCL-NOS	Brentuximab vedotin/CHP	29	19 (65.5)	21.2 [7.66, 36.2]	0.75
	CHOP	43	31 (72.1)	11.4 [6.80, 19.6]	[0.41, 1.37]
AITL	Brentuximab vedotin/CHP	30	18 (60.0)	13.9 [5.62, NE]	1.40
	CHOP	24	13 (54.2)	47.6 [14.6, NE]	[0.64, 3.07]
ATLL	Brentuximab vedotin/CHP	4	2 (50.0)	NE [2.76, NE]	0.76
	CHOP	3	2 (66.7)	6.34 [2.86, NE]	[0.10, 5.51]
Enteropathy-associated T-cell lymphoma	Brentuximab vedotin/CHP	1	1 (100)	2.50 [NE, NE]	NE
	CHOP	2	2 (100)	11.1 [6.47, 15.8]	[NE, NE]

*No patients with hepatosplenic T-cell lymphoma were enrolled in Study 014.

In addition, Part A of Study 012 in adults with relapsed or refractory CD30-positive PTCL was conducted in patients with PTCL of histopathological types other than sALCL. The PTCL histopathological types of patients enrolled in Study 012 included (a) PTCL-NOS (22 patients) and (b) AITL (13 patients), and the investigator-assessed response rates according to the IWG criteria in efficacy-evaluable patients were (a) 33.3% (7 of 21 patients) and (b) 53.8% (7 of 13 patients).

Although a precise efficacy evaluation is difficult for histopathological types which were not included or with a small number of patients enrolled in Study 014 or Part A of Study 012, the use of brentuximab vedotin for patients with such PTCL histopathological types is acceptable in view of the following observations.

- The clinical benefit of brentuximab vedotin/CHP was demonstrated in the entire patient population of Study 014. In addition, the PFS in each histopathological subpopulation did not clearly differ from that in the entire patient population.
- The results from Part A of Study 012 showed that brentuximab vedotin had a certain level of efficacy in the treatment of patients with PTCL of histopathological types other than sALCL (i.e., PTCL-NOS and AITL).
- The diagnosis and treatment system of PTCL is common to all histopathological types.

PMDA asked the applicant to explain the use of brentuximab vedotin for children with relapsed or refractory CD30-positive PTCL of histological types other than sALCL, who were not included in Studies C25002 and BV-HLALCL.

The applicant's explanation:

Because PTCL with histopathological types other than ALCL are extremely rare in children, Studies C25002 and BV-HLALCL enrolled children with sALCL. However, in view of the following observations, brentuximab vedotin monotherapy is likely to clinically benefit children with relapsed or refractory CD30-

positive PTCL of histopathological types other than sALCL, as in adults with relapsed or refractory CD30-positive PTCL.

- Brentuximab vedotin monotherapy is expected to clinically benefit adults with relapsed or refractory CD30-positive PTCL, irrespective of its histopathological type [see Table 20].
- There are no clear differences between adults and children in the diagnosis, pathological condition, and treatment system for PTCL, as well as in the PK of brentuximab vedotin [see Section 6 R.1].

PMDA's view:

In Japan, the treatment system for ATLL is partially different from that for other histopathological types of PTCL [see Section 7.R.4.1]. Nevertheless, there is little necessity to exclude ATLL from the indication of brentuximab vedotin, based on the explanation of the applicant above and in view of the following observations. Accordingly, it is possible to define the indication of brentuximab vedotin as CD30-positive PTCL including ATLL and other histopathological types. However, histopathological type-based efficacy data need to be provided to healthcare professionals.

- At present, brentuximab vedotin/CHP is the only treatment regimen that has a potential to prolong OS in patients with PTCL.
- The extremely limited number of patients with PTCL precludes the feasibility of a clinical study to evaluate histopathological type-based efficacy, etc. of brentuximab vedotin.
- Brentuximab vedotin is presumed to be prescribed by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.5 Dosage and administration

The proposed dosage and administration for brentuximab vedotin was as follows:

Dosage and Administration

Previously untreated CD30-positive PTCL

In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient's condition.

Relapsed or refractory CD30-positive PTCL

The usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

Relapsed or refractory CD30-positive HL or ALCL

The usual dosage for young children and children is 1.8 mg/kg (body weight) of Brentuximab Vedotin (Genetical Recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

The “Precautions Concerning Dosage and Administration” section included the following cautionary advice in addition to that on the approved indications.

- Dose adjustment criteria for patients with previously untreated CD30-positive PTCL to be followed in case of an adverse drug reaction

PMDA’s conclusion:

Based on the reviews in Sections “7.R.2 Efficacy,” “7 R.3 Safety,” and “7.R.4 Clinical positioning and indications,” and the subsections below, the “Dosage and Administration” and “Precautions Concerning Dosage and Administration” sections should present the following descriptions respectively.

Dosage and Administration

Previously untreated CD30-positive PTCL

In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient’s condition.

Relapsed or refractory CD30-positive HL and PTCL

The usual dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient’s condition.

Precautions Concerning Dosage and Administration

- Preparation of injectable solution and infusion duration
- The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established in the treatment of relapsed or refractory CD30-positive HL and PTCL.
- In case of an adverse drug reaction, brentuximab vedotin treatment should be delayed, reduced in dose, or discontinued by referring to the following criteria:

Neutropenia (for all indications)

Neutrophil count	Measures
$\geq 1000/mm^3$	Continue dosing at the same dose regimen.
$<1000/mm^3$	Hold dosing until it improves to baseline or $\geq 1000/mm^3$.

Peripheral neuropathy (previously untreated CD30-positive PTCL)

Grade	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Sensory neuropathy: Continue dosing at the same dose regimen. Motor neuropathy: Continue dosing at a reduced dose of 1.2 mg/kg.
Grade 3 (interfering with activities of daily living)	Sensory neuropathy: Continue dosing at a reduced dose of 1.2 mg/kg. Motor neuropathy: Discontinue dosing.
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

Peripheral neuropathy (relapsed or refractory HL and PTCL)

Grade	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Hold dosing until it improves to baseline or Grade ≤1. After recovery, resume treatment at a reduced dose of 1.2 mg/kg.
Grade 3 (interfering with activities of daily living)	
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

Grade is based on NCI-CTCAE.

7.R.5.1 Dosage and administration

The applicant's explanation about the dosage regimen of brentuximab vedotin:

(a) Dosage regimen for adults with CD30-positive PTCL:

The foreign phase I study in patients with previously untreated CD30-positive PTCL (Study 011) demonstrated the tolerability of brentuximab vedotin administered intravenously at 1.8 mg/kg in combination with CHOP. Based on this, the dosage regimen of brentuximab vedotin for Study 014 was determined to be a single intravenous dose of 1.8 mg/kg administered on Day 1 of each 21-day cycle in combination with CHP. Study 014 demonstrated clinical benefit of brentuximab vedotin in combination with CHP in patients with previously untreated CD30-positive PTCL [see Sections 7.R.2 and 7.R.3]. The proposed dosage regimen of brentuximab vedotin for the treatment of patients with previously untreated CD30-positive PTCL was based on the dosage regimen used in Study 014.

The dosage regimen of brentuximab vedotin for the treatment of patients with relapsed or refractory CD30-positive PTCL was determined as 1.8 mg/kg every 3 weeks based on that of brentuximab vedotin monotherapy for ALCL, the approved indication, and that used in Part A of Study 012.

(b) Dosage regimen for children with relapsed or refractory CD30-positive HL or ALCL:

In the Phase I part of Study C25002, brentuximab vedotin 1.4 or 1.8 mg/kg administered every 3 weeks did not reach the MTD. Based on this result, the recommended dose of brentuximab vedotin for adults with relapsed or refractory CD30-positive HL or ALCL in the Phase II part of the study was determined as 1.8 mg/kg every 3 weeks. As a result, the Phase II part of Study C25002 demonstrated clinical benefit of brentuximab

vedotin monotherapy. The dosage regimen for children with relapsed or refractory CD30-positive HL or ALCL was determined based on the dosage regimen used in the Phase II part of Study C25002.

PMDA's view:
PMDA accepted the applicant's explanation about the dosage regimen of brentuximab vedotin in general. However, the dosage regimen for the treatment of relapsed or refractory CD30-positive HL or PTCL for adults and children should be defined collectively for the following reasons: (a) Brentuximab vedotin monotherapy is expected to clinically benefit not only children with sALCL but also children with PTCL of other histopathological types [see Section 7.R.4.2]; and, (b) the dosage regimen of brentuximab vedotin monotherapy for the treatment of relapsed or refractory CD30-positive HL or PTCL is the same for adults and children.

7.R.5.2 Dose adjustment of brentuximab vedotin

PMDA asked the applicant to explain the dose adjustment of brentuximab vedotin.

The applicant's explanation:
In Study 014, the Phase II part of Study C25002, and Part A of Study 012 involving patients with PTCL employed the prespecified recommended criteria for discontinuation, dose delay, and dose reduction. These studies demonstrated the tolerability of brentuximab vedotin administered according to the criteria. Accordingly, the description of the "Precautions Concerning Dosage and Administration" section was modified as explained below, and the dose adjustment criteria were proposed based on the criteria used in the studies.

- Neutropenia:
  The Phase II part of Study C25002 had no prespecified dose adjustment criteria for neutropenia but required a neutrophil count of ≥1,000/mm^3 for starting the next cycle. In Study 012, a dose reduction from 1.8 mg/kg to 1.2 mg/kg needed to be considered following Grade 4 neutropenia occurring despite G-CSF prophylaxis; however, no patients experienced such event. Based on these results, the dose adjustment criteria for neutropenia set for the approved indications was also proposed for the additional indication.
- Thrombocytopenia:
  In the Phase II part of Study C25002, a dose reduction from 1.8 mg/kg to 1.2 mg/kg was allowed following Grade 4 thrombocytopenia persisting for >7 days; however, no patients experienced such event. Therefore, no dose adjustment criteria were proposed for thrombocytopenia.
- Non-hematological toxicities other than peripheral neuropathy:
  In Study 014, no dose adjustment criteria were prespecified in case of non-hematological toxicities other than peripheral neuropathy, and the respective study sites were required to take appropriate measures for such events by their own guidelines. Given this, no criteria were proposed for dose adjustment after the onset of non-hematological toxicities other than peripheral neuropathy. In the Phase II part of Study C25002 as well as Study 012, the dose of brentuximab vedotin was adjusted by dose delay, dose reduction, or discontinuation following Grade ≥3 adverse events. Nevertheless, with the prospect that a decision on dose adjustment be made by the physician according to patient's condition, no dose adjustment criteria were proposed for the relevant adverse events of Grade ≥3 in the present partial change application.

PMDA accepted the applicant's explanation.

7.R.5.3 Concomitant antineoplastic drugs and brentuximab vedotin monotherapy

The applicant's explanation about brentuximab vedotin administered alone to patients with previously untreated CD30-positive PTCL, and in combination with other antineoplastic drugs to patients with relapsed or refractory CD30-positive PTCL:

There are no clinical study results demonstrating the clinical benefit of brentuximab vedotin monotherapy in the treatment of previously untreated CD30-positive PTCL. Therefore, the use of brentuximab vedotin alone is not recommended for the treatment of previously untreated CD30-positive PTCL.

Furthermore, there are no clinical study results demonstrating the clinical benefit of brentuximab vedotin administered in combination with other antineoplastic drugs in the treatment of relapsed or refractory CD30-positive PTCL. Therefore, as with the previously approved indication of ALCL, brentuximab vedotin with other antineoplastic drugs is not recommended for the treatment of relapsed or refractory CD30- positive PTCL.

Based on the above, appropriate concomitant antineoplastic drugs for the treatment of previously untreated CD30-positive PTCL will be clearly specified in the dosage regimen of brentuximab vedotin. For the treatment of relapsed or refractory CD30-positive PTCL, the following current cautionary advice on the concomitant use of other antineoplastic drugs for the approved indication will remain in the "Precautions Concerning Dosage and Administration" section, while the term "ALCL" will be replaced with "PTCL."

- The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established in the treatment of relapsed or refractory CD30-positive HL or ALCL.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

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

The applicant will conduct (a) all-case post-marketing surveillance in patients with previously untreated CD30-positive PTCL, and (b) all-case post-marketing surveillance in patients with relapsed or refractory CD30-positive HL or PTCL (except adult patients treated for the approved indications of HL or ALCL), as per the plan below. The purpose of these surveillances is to evaluate the safety, etc. of brentuximab vedotin in its clinical use.

(a) All-case post-marketing surveillance in patients with previously untreated CD30-positive PTCL:

- The proposed safety specification is bone marrow depression (neutropenia and febrile neutropenia) based on the incidences of adverse events in the brentuximab vedotin/CHP group of Study 014. The proposed target sample size is 50 patients based on the incidence of febrile neutropenia in the brentuximab vedotin/CHP group of Study 014, etc.

- The proposed observation period begins with the start of treatment with brentuximab vedotin and ends at 3 weeks after the eighth dose, in view of the period of time from the first onset to the resolution of febrile neutropenia in the brentuximab vedotin/CHP group of Study 014.

(b) All-case post-marketing surveillance in patients with relapsed or refractory CD30-positive HL or PTCL (except adult patients treated for the approved indications of HL and ALCL):

- The proposed safety specification includes neuropathy peripheral, bone marrow depression (neutropenia), and lung disorders, which are the events of special interest in patients treated with brentuximab vedotin.
- The proposed target sample size for adult patients is 80 based on the incidences of adverse events (neuropathy peripheral, bone marrow depression [neutropenia], lung disorders, etc.) in the specified use-results survey, in adult patients with relapsed or refractory CD30-positive HL or ALCL. The proposed target sample size for pediatric patients is 6 in view of feasibility based on the estimated number of children with relapsed or refractory HL or PTCL, the proposed observation period, and other factors.
- The proposed observation period is 12 months beginning at the start of treatment with brentuximab vedotin, in view of the time of onset of adverse events revealed by the specified use-results survey in patients with relapsed or refractory CD30-positive HL or ALCL, etc.

PMDA's view:

(a) All-case post-marketing surveillance in patients with previously untreated CD30-positive PTCL:

In view of the observations below, there is little necessity to conduct the surveillance immediately after approval, and safety information of brentuximab vedotin/CHP can be collected through routine pharmacovigilance activity.

- The incidences of neutropenia and febrile neutropenia in the brentuximab vedotin/CHP group of Study 014 tended to be lower than those in patients treated with brentuximab vedotin in combination with doxorubicin, vincristine, and dacarbazine (AVD) for the approved indication of previously untreated CD30-positive HL in Study C25003.
- The results of the review in Section "7.R.3 Safety" identified no new safety concerns for the present partial change application.
- A certain amount of safety data of brentuximab vedotin are available from Japanese patients through the completed specified use-results survey in adults with relapsed or refractory CD30-positive HL or ALCL, which identified no new events subject to cautionary advice, and the ongoing post-marketing surveillance in patients with previously untreated CD30-positive HL.

(b) All-case post-marketing surveillance in patients with relapsed or refractory CD30-positive HL or PTCL (except [treated for the approved indications of HL and ALCL):

Due to the small number of Japanese patients who have been treated with brentuximab vedotin for relapsed or refractory CD30-positive HL or PTCL, post-marketing surveillance should be conducted involving this patient population, and available safety information should be promptly provided to healthcare professionals. However, in view of the following observations, there is little necessity for the surveillance to cover all patients treated with brentuximab vedotin for the intended indication, as long as safety information on the use of brentuximab

vedotin in Japanese patients with relapsed or refractory CD30-positive HL or PTCL is appropriately collected and disseminated.

- Major adverse events reported in Study 012 were known events of brentuximab vedotin administered for the approved indications [see Section 7.R.3.1].
- A certain amount of safety data of brentuximab vedotin are available from Japanese patients through the completed specified use-results survey in adults with relapsed or refractory CD30-positive HL or ALCL, which identified no new events subject to cautionary advice.
- There have been no adverse events that are specific to children as compared with adults [see Section 7.R.3].

The proposed safety specifications, target sample size, and observation period for (b) are acceptable.

7.2 Adverse events reported in clinical studies

Based on the clinical study results submitted for the safety evaluation, death-related results are presented in "Section 7.1 Evaluation data," while other major adverse events are summarized below.

7.2.1 Global phase III study (Study 014)

Adverse events were reported in 221 of 223 patients (99.1%) in the brentuximab vedotin/CHP group, and 221 of 226 patients (97.8%) in the CHOP group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 210 of 223 patients (94.2%) in the brentuximab vedotin/CHP group, and 212 of 226 patients (93.8%) in the CHOP group. The adverse events reported with a ≥10% incidence in either treatment group are shown in Table 21.

Table 21. Adverse events reported with a ≥10% incidence in either treatment group

SOC PT (MedDRA/J ver.21.0)	n (%)			
	Brentuximab vedotin/CHP N = 223		CHOP N = 226	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	221 (99.1)	147 (65.9)	221 (97.8)	146 (64.6)
Blood and lymphatic system disorders				
Neutropenia	85 (38.1)	77 (34.5)	85 (37.6)	76 (33.6)
Anaemia	46 (20.6)	30 (13.5)	36 (15.9)	23 (10.2)
Febrile neutropenia	41 (18.4)	41 (18.4)	33 (14.6)	33 (14.6)
Gastrointestinal disorders				
Nausea	103 (46.2)	5 (2.2)	87 (38.5)	4 (1.8)
Constipation	64 (28.7)	2 (0.9)	67 (29.6)	3 (1.3)
Diarrhoea	85 (38.1)	13 (5.8)	46 (20.4)	2 (0.9)
Vomiting	57 (25.6)	2 (0.9)	39 (17.3)	4 (1.8)
Stomatitis	27 (12.1)	3 (1.3)	27 (11.9)	3 (1.3)
General disorders and administration site conditions				
Fatigue	54 (24.2)	2 (0.9)	46 (20.4)	4 (1.8)
Pyrexia	58 (26.0)	4 (1.8)	42 (18.6)	0
Asthenia	26 (11.7)	2 (0.9)	16 (7.1)	0
Peripheral oedema	24 (10.8)	0	18 (8.0)	2 (0.9)
Investigations				
Weight decreased	26 (11.7)	1 (0.4)	17 (7.5)	1 (0.4)
Metabolism and nutrition disorders				
Decreased appetite	39 (17.5)	3 (1.3)	27 (11.9)	3 (1.3)
Hypokalaemia	27 (12.1)	8 (3.6)	18 (8.0)	3 (1.3)
Musculoskeletal and connective tissue disorders				
Myalgia	24 (10.8)	0	19 (8.4)	0
Nervous system disorders				
Peripheral sensory neuropathy	100 (44.8)	8 (3.6)	92 (40.7)	6 (2.7)
Headache	31 (13.9)	1 (0.4)	31 (13.7)	1 (0.4)
Dizziness	28 (12.6)	0	20 (8.8)	2 (0.9)
Psychiatric disorders				
Insomnia	25 (11.2)	0	31 (13.7)	0
Respiratory, thoracic, and mediastinal disorders				
Dyspnoea	32 (14.3)	4 (1.8)	24 (10.6)	4 (1.8)
Cough	27 (12.1)	2 (0.9)	22 (9.7)	0
Skin and subcutaneous tissue disorders				
Alopecia	58 (26.0)	0	56 (24.8)	3 (1.3)

Serious adverse events were reported in 87 of 223 patients (39.0%) in the brentuximab vedotin/CHP group, and 87 of 226 patients (38.5%) in the CHOP group. The serious adverse events reported by ≥5 patients in the brentuximab vedotin/CHP group were febrile neutropenia in 31 patients (13.9%), pneumonia in 11 patients (4.9%), pyrexia in 9 patients (4.0%), neutropenia in 8 patients (3.6%), and pneumonitis and sepsis in 5 patients (2.2%) each. The serious adverse events reported by ≥5 patients in the CHOP group were febrile neutropenia in 26 patients (11.5%), anaplastic large cell lymphoma T- and null-cell types in 11 patients (4.9%), pyrexia in 7 patients (3.1%), neutropenia in 6 patients (2.7%), and pulmonary embolism in 5 patients (2.2%). A causal relationship to the study drug could not be ruled out for febrile neutropenia in 29 patients, pneumonia in 9 patients, neutropenia in 8 patients, sepsis in 4 patients, and pyrexia and pneumonitis in 3 patients each in the brentuximab vedotin/CHP group, and febrile neutropenia in 26 patients, neutropenia in 6 patients, and pyrexia in 2 patients in the CHOP group.

Adverse events led to treatment discontinuation in 16 of 223 patients (7.2%) in the brentuximab vedotin/CHP group and 19 of 226 patients (8.4%) in the CHOP group. The adverse events leading to treatment discontinuation in ≥2 patients in either treatment group were peripheral sensory neuropathy in 4 patients (1.8%) in the brentuximab vedotin/CHP group, and peripheral sensory neuropathy in 4 patients (1.8%), and sepsis, anaplastic large cell lymphoma T- and null-cell types, and peripheral motor neuropathy in 2 patients (0.9%) each in the CHOP group. A causal relationship to the study drug could not be ruled out for the peripheral sensory neuropathy in 3 patients in the brentuximab vedotin/CHP group, and peripheral sensory neuropathy in 4 patients, and sepsis and peripheral motor neuropathy in 2 patients each in the CHOP group.

7.2.2 Foreign phase I study (Study 011)

Adverse events were reported in all 39 patients (100%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported in 38 of 39 patients (97.4%). The adverse events reported with a ≥30% incidence were nausea and peripheral sensory neuropathy in 28 patients (71.8%) each, fatigue in 23 patients (59.0%), diarrhoea and alopecia in 19 patients (48.7%), dyspnoea in 18 patients (46.2%), constipation in 15 patients (38.5%), oedema peripheral and myalgia in 13 patients (33.3%) each, and anaemia, vomiting, and chills in 12 patients (30.8%) each.

Serious adverse events were reported in 19 of 39 patients (48.7%). The serious adverse events reported by ≥2 patients were febrile neutropenia in 10 patients (25.6%), pyrexia in 3 patients (7.7%), and cardiac failure, pneumocystis jirovecii pneumonia, sepsis, and urinary tract infection in 2 patients (5.1%) each. A causal relationship to the study drug could not be ruled out for the febrile neutropenia in 8 patients, pneumocystis jirovecii pneumonia, sepsis, and urinary tract infection in 2 patients each, and pyrexia and cardiac failure in 1 patient each.

The adverse event leading to treatment discontinuation was eye pruritus in 1 patient (2.6%), for which a causal relationship to the study drug could not be ruled out.

7.2.3 Foreign phase II study (Study 012)

Adverse events were reported in 32 of 35 patients (91.4%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 28 of 35 patients (80.0%). The adverse events reported with a ≥20% incidence were peripheral sensory neuropathy in 13 patients (37.1%), fatigue in 12 patients (34.3%), pyrexia in 8 patients (22.9%), and decreased appetite in 7 patients (20.0%).

Serious adverse events were reported in 15 of 35 patients (42.9%). The serious adverse events reported by ≥2 patients were acute kidney failure, confusional state, dehydration, pneumonia, and pyrexia in 2 patients (5.7%) each. A causal relationship to the study drug could not be ruled out for the pneumonia and pyrexia in 1 patient each. The adverse event leading to treatment discontinuation or dose reduction in ≥2 patients was peripheral sensory neuropathy in 3 patients (8.6%).

7.2.4 Japan phase I study (Study BV-HLALCL)

All 6 patients (100%) reported adverse events and adverse events for which a causal relationship to the study drug could not be ruled out. The adverse events reported with a ≥50% incidence were white blood cell count decreased and pyrexia in 5 patients (83.3%) each, and neutrophil count decreased and upper respiratory tract infection in 3 patients (50.0%) each.

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.2.5 Foreign phase I/II study (Study C25002)

Adverse events were reported in all 36 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 25 of 36 patients (69.4%). The adverse events reported with a ≥20% incidence were pyrexia in 16 patients (44.4%) and nausea in 13 patients (36.1%).

Serious adverse events were reported in 8 of 36 patients (22.2%). The serious adverse event reported by ≥2 patients was pyrexia in 2 patients (5.6%). A causal relationship to the study drug could be ruled out in both of these patients.

Adverse events led to treatment discontinuation in 2 of 36 patients (5.6%). These adverse events were cardiac arrest and hepatotoxicity in 1 patient (2.8%) each. A causal relationship to the study drug could not be ruled out for the hepatotoxicity.

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 inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that brentuximab vedotin has efficacy in the treatment of CD30-positive HL and PTCL, and that brentuximab vedotin has acceptable safety in view of its benefits. Brentuximab vedotin is clinically meaningful because it offers a new therapeutic option for patients with CD30-positive HL or PTCL. The clinical positioning, indications, and dosage and administration should be further discussed.

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

Review Report (2)

November 5, 2019

Product Submitted for Approval

Brand Name	Adcetris for Intravenous Drip Infusion 50 mg
Non-proprietary Name	Brentuximab Vedotin (Genetical Recombination)
Applicant	Takeda Pharmaceutical Company Limited
Date of Application	March 29, 2019

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 a result of its review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA reached the following conclusions on (a) the treatment with brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for adults with previously untreated CD30-positive peripheral T-cell lymphoma (PTCL), and (b) brentuximab vedotin monotherapy for children with relapsed or refractory CD30-positive Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL).

(a) The efficacy of brentuximab vedotin/CHP was demonstrated in the treatment of adults with previously untreated CD30-positive PTCL by the results from a global phase III study conducted in this patient population (Study 014), primarily based on the superiority of brentuximab vedotin/CHP in the primary endpoint (i.e., PFS assessed according to the International Working Group [IWG] criteria) over cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

(b) A certain level of efficacy of brentuximab vedotin monotherapy was demonstrated in the treatment of children with relapsed or refractory CD30-positive HL or ALCL by the results from the Phase II part of a foreign phase I/II study in patients with relapsed or refractory HL or sALCL aged ≥2 to <18 years (Study C25002), primarily based on the satisfactory response to the monotherapy.

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

1.2 Safety

As a result of its review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that the brentuximab vedotin-associated adverse events requiring particular attention in adults with CD30-positive PTCL and children with relapsed or refractory CD30-positive HL or ALCL are infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome, lung disorders, pancreatitis acute, and hepatic dysfunction. These are known adverse events of brentuximab vedotin warranting attention, which were identified during the review process for the approved indications.

PMDA also concluded that despite these adverse events warranting attention, brentuximab vedotin is tolerable in adults with CD30-positive PTCL and in children with relapsed or refractory CD30-positive HL or ALCL, given appropriate measures, i.e., monitoring and management of adverse events, dose delay, etc. taken by physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

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

1.3 Clinical positioning and indication

As a result of its review in Section "7.R.4 Clinical positioning and indications" of the Review Report (1), PMDA concluded that brentuximab vedotin will deserve recognition as a treatment option for patients with CD30-positive HL or PTCL, and that the indication of brentuximab vedotin should be described as "The following CD30-positive diseases: Hodgkin's lymphoma, Peripheral T-cell lymphoma" as proposed by the applicant, with the following cautionary advice provided in the "Precautions Concerning Indications" section, which remains unchanged from that for the approved indications.

- Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
- Brentuximab vedotin should be used in who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

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

Accordingly, PMDA instructed the applicant to define the "Indications" and "Precautions Concerning Indications" in the respective sections. The applicant agreed.

1.4 Dosage and Administration

As a result of its review in Section "7.R.5 Dosage and Administration" of the Review Report (1), PMDA concluded that the "Dosage and Administration" and the "Precautions Concerning Dosage and Administration" be defined as below in the respective sections for the present partial change application.

Dosage and Administration

Previously untreated CD30-positive peripheral T-cell lymphoma

In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient's condition.

Relapsed or refractory CD30-positive Hodgkin's lymphoma and peripheral T-cell lymphoma

The usual dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

Precautions Concerning Dosage and Administration

- Preparation of injectable solution and infusion duration.
- The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established in the treatment of relapsed or refractory CD30-positive HL and PTCL.
- Criteria for dose delay, dose reduction, and treatment discontinuation upon the occurrence of adverse drug reactions

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

Based on the above, PMDA instructed the applicant to define the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" in the respective sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant's plan for post-marketing surveillance for brentuximab vedotin is as follows:

(a) All-case post-marketing surveillance in patients with previously untreated CD30-positive PTCL

- Safety specification, Bone marrow depression (neutropenia and febrile neutropenia)
- Target sample size, 50 patients
- Observation period, From the start of treatment with brentuximab vedotin to 3 weeks after the eighth dose

(b) All-case post-marketing surveillance in patients with relapsed or refractory CD30-positive HL or PTCL (except adult patients treated for the approved indications of HL or ALCL)

- Safety specifications, Neuropathy peripheral, bone marrow depression (neutropenia), and lung disorders
- Target sample size, 80 adults and 6 children
- Observation period, 12 months

In view of the discussion in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA reached the following conclusions on the above post-marketing surveillance (a) and (b).

- (a) There is little necessity to conduct the surveillance immediately after approval. The routine pharmacovigilance activities will sufficiently serve to gather safety information of the brentuximab vedotin/CHP regimen.
- (b) The surveillance should be conducted and available safety information should be provided promptly to healthcare professionals. However, there is little necessity for the surveillance to cover all patients treated with brentuximab vedotin for the intended indication, as long as safety data are appropriately collected and disseminated. The safety specification, target sample size, and observation period proposed by the applicant are acceptable.

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

In view of the discussion above, PMDA concluded that the drafted risk management plan for brentuximab vedotin should include the safety specification presented in Table 22, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 23 and 24.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Neuropathy peripheral • Infections • Progressive multifocal leukoencephalopathy • Bone marrow suppression • Infusion reaction • Tumour lysis syndrome • Stevens-Johnson syndrome • Acute pancreatitis • Hepatic dysfunction • Lung disorder	• Gastrointestinal disorder • Reproductive toxicity • Depletion of thymic lymphoid tissue • Interactions with CYP3A4 inhibitors	None
Efficacy specification		
None		

No changes in the present partial change application

Table 23. 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
• General use-results survey in patients with previously untreated CD30-positive HL • Special use-results survey in patients with relapsed or refractory CD30-positive HL and PTCL • Post-marketing clinical studies (extension studies of Studies C25003 and 014)	None	• Organize and disseminate information for healthcare professionals

Underline denotes activities to be implemented for the new indication and dosage regimen.

Table 24. Outline of post-marketing surveillance (draft)

Objective	To evaluate the safety, etc. of brentuximab vedotin in patients with relapsed or refractory CD30-positive HL or PTCL in post-marketing clinical use
Survey method	Central registration system
Population	Patients with relapsed or refractory CD30-positive HL or PTCL (except adult patients with HL or ALCL)
Observation period	12 months after the start of brentuximab vedotin therapy
Planned sample size	80 adults and 6 children
Main survey items	Safety specification: Neuropathy peripheral, bone marrow depression (neutropenia), and lung disorders Other main survey items: patient characteristics (e.g., age, gender, prior treatments, diagnosis, clinical stage, PTCL histopathological type), exposure to brentuximab vedotin, concomitant medications, and other relevant items

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

2.1 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.

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

The new drug application data (CTD 5.3.5.1-1 and 5.3.5.2-3) 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. Meanwhile, the inspection revealed the following finding at some study sites. Although the error did not affect the evaluation, it was notified to the heads of the study sites concerned and the sponsor to request a corrective action.

Finding requiring corrective action

Study sites

- A writing error in the outsourcing contract on the partial transfer of duties in the clinical studies

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and the dosage and administration refined as below with the following approval condition. The approval, however, presupposes appropriate advice given through the package insert, appropriate information provision on the proper use of the product in the post-marketing setting, and adherence to the proper use of the product under the supervision of physicians with sufficient knowledge and experience in the treatment of hematopoietic malignancies at medical institutions that are fully capable of responding to emergencies. The re-examination period for the present partial change approval is the remainder of the ongoing re-examination period for the initial approval (until January 16, 2024).

Indications (Underline denotes additions and strikethrough denotes deletions.)

The following CD30-positive diseases:

○Hodgkin's lymphoma

○Peripheral T-cell lymphoma

~~○Relapsed or refractory anaplastic large-cell lymphoma~~

Dosage and Administration (Underline denotes additions and strikethrough denotes deletions.)

1. Previously untreated CD30-positive Hodgkin's lymphoma

In combination with doxorubicin hydrochloride, vinblastine sulfate, and dacarbazine, the usual adult dosage is 1.2 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 2 weeks for up to 12 doses. The dose may be reduced as appropriate according to the patient's condition.

2. Previously untreated CD30-positive peripheral T-cell lymphoma

In combination with cyclophosphamide hydrate, doxorubicin hydrochloride, and prednisolone, the usual adult dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks for up to 8 doses. The dose may be reduced as appropriate according to the patient's condition.

3. Relapsed or refractory CD30-positive Hodgkin's lymphoma and peripheral T-cell lymphoma ~~anaplastic large-cell lymphoma~~

The usual ~~adult~~ dosage is 1.8 mg/kg (body weight) of brentuximab vedotin (genetical recombination) administered as an intravenous infusion every 3 weeks. The dose may be reduced as appropriate according to the patient's condition.

Approval Condition

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

Warnings (No change)

1. The product should be administered only to patients considered eligible for brentuximab vedotin therapy under the supervision of a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies at a medical institution well-equipped to cope with emergencies. Consent should be obtained, prior to treatment, from the patient or his/her family member who has been fully informed of the benefits and risks of the therapy.
2. Fungal infection with a fatal outcome after administration of brentuximab vedotin in patients with moderate or severe hepatic impairment has been reported from foreign clinical studies. The use of brentuximab vedotin should be carefully determined in these patients.

Contraindications (Underline denotes additions.)

1. Patients with a history of severe hypersensitivity to any ingredients of the product
2. Patients who are receiving bleomycin hydrochloride

Precautions Concerning Indications (No change)

1. Eligible patients should be selected by physicians with full knowledge of the information in the "CLINICAL STUDIES" section and sufficient understanding of the efficacy and safety of brentuximab vedotin.
2. Brentuximab vedotin should be used in who are confirmed to be positive for CD30 antigen with the immunohistological or other methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

Precautions Concerning Dosage and Administration (Underline denotes additions and strikethrough denotes deletions.)

For all indications

1. The diluted solution should be intravenously infused over at least 30 minutes.
2. If neutropenia occurred ~~after administration of brentuximab vedotin~~, patients should have dose delay~~, dose reduction, or discontinuation~~ by referring to the following criteria:

Neutrophil count ~~Grade *Note~~	Measures
≥1000/mm^3 ~~Grade 1 (< LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)~~	Continue dosing at the same dose regimen.
< 1000/mm^3 ~~Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)~~	Hold dosing until it improves to ~~Grade ≤2 or~~ baseline or ≥1000/mm^3. ~~After recovery, resume treatment at the same dose regimen.~~

Previously untreated CD30-positive Hodgkin's lymphoma

3. If peripheral neuropathy occurred ~~after administration of brentuximab vedotin~~, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Grade*Note	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Continue dosing at a reduced dose of 0.9 mg/kg.
Grade 3 (interfering with activities of daily living)	Hold dosing until it improves to Grade ≤2. After recovery, resume treatment at a reduced dose of 0.9 mg/kg. Consider dose reduction of a neurotoxic concomitant agent, if any, referring to the package insert.
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

Previously untreated CD30-positive peripheral T-cell lymphoma

4. If peripheral neuropathy occurred, patients should have dose reduction or discontinuation by referring to the following criteria.

Grade*Note	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Sensory neuropathy: Continue dosing at the same dose regimen. Motor neuropathy: Continue dosing at a reduced dose of 1.2 mg/kg.
Grade 3 (interfering with activities of daily living)	Sensory neuropathy: Continue dosing at a reduced dose of 1.2 mg/kg. Motor neuropathy: Discontinue dosing.
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

Relapsed or refractory CD30-positive Hodgkin's lymphoma and peripheral T-cell lymphoma ~~anaplastic large-cell lymphoma~~

5~~4~~. The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established.

6~~5~~. If neuropathy peripheral occurred ~~after administration of brentuximab vedotin~~, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Grade*Note	Measures
Grade 1 (loss of reflexes or paresthesia but not interfering with function)	Continue dosing at the same dose regimen.
Grade 2 (interfering with function, but not interfering with activities of daily living)	Hold dosing until it improves to baseline or Grade ≤1. After recovery, resume treatment at a reduced dose of 1.2 mg/kg.
Grade 3 (interfering with activities of daily living)	
Grade 4 (disabling sensory neuropathy, or life-threatening or paralytic motor neuropathy)	Discontinue dosing.

* Based on NCI-CTCAE ~~v3.0~~

Appendix

List of Abbreviations

AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
AMP	doxorubicin, ranimustine, and prednisolone
ASCO	American Society of Clinical Oncology
ATLL	adult T-cell leukemia/lymphoma
AVD	doxorubicin, vinblastine, and dacarbazine
brentuximab vedotin	brentuximab vedotin (genetic recombination)
brentuximab vedotin/CHP	brentuximab vedotin and CHP
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisone
CHP	cyclophosphamide, doxorubicin and prednisone
CI	confidential interval
CR	complete remission
cyclophosphamide	cyclophosphamide hydrate
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
doxorubicin	doxorubicin hydrochloride
ESMO	European Society for Medical Oncology
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyltransferase
HL	Hodgkin lymphoma
IPI	International Prognostic Index
ITT	intent-to-treat
IWG	International Working Group
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mLSG15 therapy	modified LSG15 therapy
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHL	non-Hodgkin lymphoma
OS	overall survival
Partial change application	Application for partial change approval
PD	progressive disease
PFS	progression free survival
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
Q3W	quaque 3 week
RIT	Rituximab
sALCL	systemic anaplastic large-cell lymphoma
SD	stable disease
SOC	system organ class

Study 0003	Study SG035-0003
Study 0004	Study SG035-0004
Study 011	Study SGN35-011
Study 012	Study SGN35-012
Study 014	Study SGN35-014
VCAP	vincristine, cyclophosphamide, doxorubicin, and prednisolone
VECP	vindesine sulfate, carboplatin, etoposide, and prednisolone
vinblastine	vinblastine sulfate
vincristine	vincristine sulfate