Report on the Deliberation Results

November 28, 2013
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[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 22, 2013

[Results of deliberation]
In the meeting held on November 18, 2013, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years, the drug substance and the drug product are both classified as a powerful drug and the product is classified as a biological product.

[Conditions for approval]
The applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated, in order to understand the characteristics of patients treated with this product, since only a limited number of Japanese patients participated in clinical studies of the product. At the same time, collect safety and efficacy data on the product without delay and take necessary measures for the proper use of the product.

**Japanese Accepted Name (modified INN)*

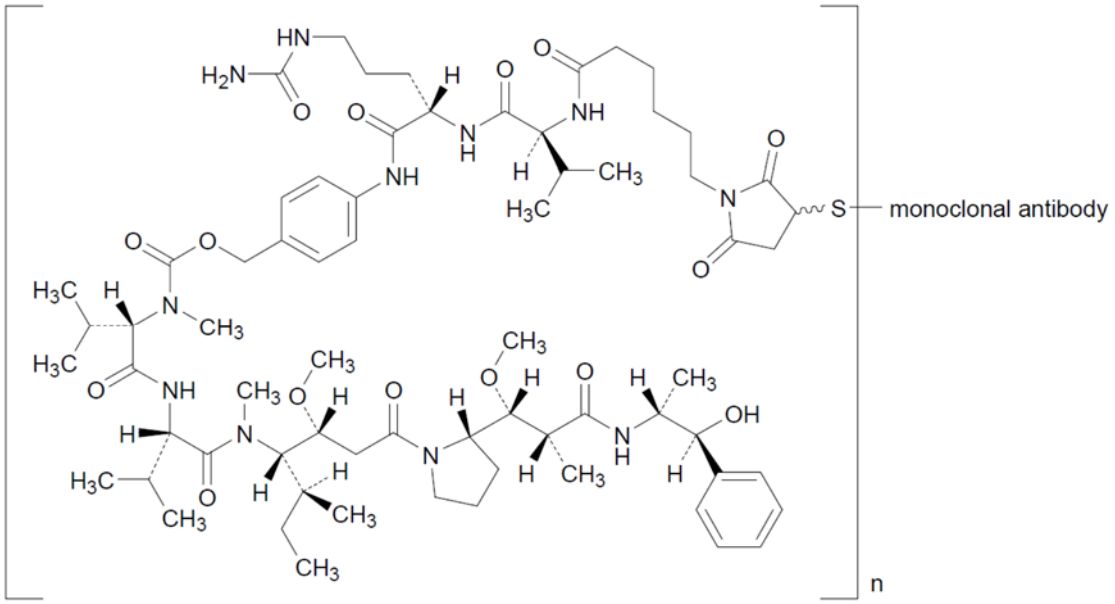
Review Report

November 8, 2013
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Adcetris for Intravenous Drip Infusion 50 mg
[Non-proprietary name]	Brentuximab Vedotin (Genetical Recombination)
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 22, 2013
[Dosage form/Strength]	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Amino acid sequences and disulfide bonds are as shown below.

[Amino acid sequence]
Light chain

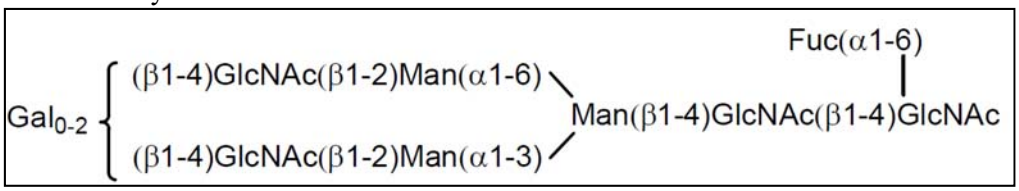
DIVLTQSPAS LAVSLGQRAT ISCKASQSVD FDGDSYMNWY QQKPGQPPKV
LIYAASNLES GIPARFSGSG SGTDFTLNIH PVEEEDAATY YCQQSNEDPW
TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV
THQGLSSPVT KSFNRGEC

Heavy chain

QIQLQQSGPE VVKPGASVKI SCKASGYTFT DYYITWVKQK PGQGLEWIGW
IYPGSGNTKY NEKFKGKATL TVDTSSSTAF MQLSSLTSED TAVYFCANYG
NYWFAYWGQG TQVTVSAAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG(K)

Intramolecular disulfide bonds: Solid lines
Intermolecular disulfide bonds: 1 (Cys^{218} in light chain - Cys^{220} in heavy chain), 2 (Cys^{226} in heavy chain - Cys^{226} in heavy chain), 3 (Cys^{229} in heavy chain - Cys^{229} in heavy chain)
Partial modification to pyroglutamate: Glu^{1} in heavy chain
Potential drug-binding sites: Cys^{218} in light chain, Cys^{220} in heavy chain, Cys^{226} in heavy chain, Cys^{229} in heavy chain
Glycosylation site: Asn^{297} in heavy chain
Partial processing: Lys^{447} in heavy chain

Main carbohydrate structure



Ga, Galactose; GlcNAc, *N*-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula:	$C_{6860}H_{10532}N_{1740}O_{2168}S_{40}$
Molecular weight:	153,352
Chemical name:	Brentuximab Vedotin is an antibody-drug-conjugate (molecular weight: ca. 153,000) consisting of Vedotin (1-(6-{[(2*S*)-1-({(2*S*)-5-carbamoylamino-1-[(4-{[(2*S*)-{[(2*S*)-1-{[(3*R*,4*S*,5*S*)-1-{(2*S*)-2-[(1*R*,2*R*)-3-{[(1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-

3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)amino}-3-methyl-1-oxobutan-2-yl]amino}-3-methyl-1-oxobutan-2-yl]methylcarbamoyloxy}methylphenyl)amino]-1-oxopentan-2-yl}amino)-3-methyl-1-oxobutan-2-yl]amino}-6-oxohexyl)-2,5-dioxopyrrolidin-3-ylgroup ($C_{68}H_{106}N_{11}O_{15}$; molecular weight: 1317.63)), which is composed of monomethyl auristatin E({(*S*)-1-[((*S*)-1-{[(3*R*,4*S*,5*S*)-1-((*S*)-2-{(1*R*,2*R*)-3-[((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)amino]-1-methoxy-2-methyl-3-oxopropyl}pyrrolidin-1-yl)-3-methoxy-5-methyl-1-oxoheptan-4-yl][methyl]amino}-3-methyl-1-oxobutan-2-yl)amino]-3-methyl-1-oxobutan-2-yl}(methyl)amine) and 4-((*S*)-2-{(*S*)-2-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanamido]-3-methylbutanamido}-5-ureidopentanamido)benzyloxycarbonyl linker, attached to an average of 3-5 Cys residues of a recombinant monoclonal antibody (molecular weight: ca. 148,000).

The monoclonal antibody moiety is a chimeric monoclonal antibody composed of variable regions derived from a mouse anti-human CD30 monoclonal antibody and constant regions derived from a human IgG1 and produced in Chinese hamster ovary cells. The protein moiety is a glycoprotein composed of 2 H-chain (γ1-chain) molecules consisting of 447 amino acid residues each and 2 L-chain (κ-chain) molecules consisting of 218 amino acid residues each.

[Items warranting special mention]

Orphan drug (Notification No. 0319-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 19, 2012)

[Reviewing office] Office of New Drug V

Review Results

November 8, 2013

[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 22, 2013

[Results of review]
Based on the submitted data, the product is expected to be effective in patients with relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma and its safety is considered acceptable in view of its observed benefits. The occurrences of infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome, lung disorder, pancreatitis acute, and hepatic function disorder need to be further investigated via post-marketing surveillance.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indications and the dosage regimen as shown below, with the following conditions.

[Indications]	The following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma
[Dosage and administration]	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.
[Conditions for approval]	The applicant is required to conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated, in order to understand the characteristics of patients treated with this product, since only a limited number of Japanese patients participated in clinical studies of the product. At the same time, collect safety and efficacy data on the product without delay and take necessary measures for the proper use of the product.

Review Report (1)

September 27, 2013

I. Product Submitted for Registration

[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 22, 2013
[Dosage form/Strength]	Injection: Powder for reconstitution before use. Each vial contains 55 mg of Brentuximab Vedotin (Genetical Recombination).
[Proposed indication]	The following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma
[Proposed dosage and administration]	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.

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

The data submitted in this application and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Drug overview

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

Brentuximab Vedotin (Genetical Recombination) (hereinafter referred to as "brentuximab vedotin") is an antibody-drug conjugate discovered by Seattle Genetics, Inc. (US). Brentuximab vedotin is composed of a chimeric monoclonal antibody, which has variable regions derived from a mouse anti-human CD30 monoclonal antibody and constant regions derived from a human immunoglobulin G1 (IgG1), and monomethyl auristatin E (MMAE), a tubulin polymerization inhibitor, which is covalently bound to the 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.

1.(2) Development history etc.

Outside Japan, a phase I study (Study SG035-0001) was initiated by Seattle Genetics, Inc. (US) in November 2006 in patients with relapsed or refractory CD30-positive haematopoietic malignancies. Subsequently, a phase II study (Study SG035-0003) was initiated in February 2009 in patients with relapsed or refractory CD30-positive HL who had undergone autologous haematopoietic stem cell transplantation, and a phase II study (Study SG035-0004) was initiated

in June 2009 in patients with relapsed or refractory CD30-positive systemic ALCL (sALCL, excluding primary cutaneous ALCL limited to the skin).

Based on data from Studies SG035-0003 and SG035-0004, a regulatory application for brentuximab vedotin was filed by Seattle Genetics, Inc. in February 2011 in the US and by Takeda Global Research and Development Centre (Europe) Ltd. in May 2011 in the EU. In the US, brentuximab vedotin was granted accelerated approval in August 2011 for the following indications: "Adcetris (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates," and "Adcetris is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen." In the EU, brentuximab vedotin was approved in October 2012 for the following indications: "Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option," and "Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)."

As of August 2013, brentuximab vedotin has been approved in 5 countries or regions for indications of HL and sALCL.

In Japan, a phase I/II study (Study TB-BC010088) was initiated by Takeda Bio Development Center Limited in October 2011 in patients with relapsed or refractory CD30-positive HL and sALCL.

Based on the pivotal study results obtained from Studies SG035-0003, SG035-0004, and TB-BC010088, a marketing approval application for brentuximab vedotin was filed in March 2013.

Brentuximab vedotin was designated as an orphan drug in March 2012 with the proposed indications for the treatment of "CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma" (Designation No. [24 yaku] No. 267).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Brentuximab Vedotin (Genetical Recombination) (hereinafter referred to as "brentuximab vedotin") is an antibody-drug conjugate prepared by reducing interchain disulfide bonds in a chimeric monoclonal antibody (cAC10), consisting of variable regions derived from a mouse monoclonal anti-human CD30 antibody and constant regions derived from a human immunoglobulin G1 (IgG1), and covalently binding the resultant thiol group to monomethyl auristatin E (MMAE), a tubulin polymerization inhibitor, via a linker containing a maleimide, caproyl spacer, valine, citrulline, and *p*-aminobenzyloxy carbonyl group.

As critical intermediates of the drug substance, cAC10 and an intermediate representing the linker-bound MMAE (SGD-1006) are controlled. The quality by design (QbD) approach has been utilized for development of the drug substance and its intermediates [see "2.A.(4) Quality by design (QbD)"].

2.A.(1).1) Anti-human CD30 monoclonal antibody (cAC10)

2.A.(1).1).i) Preparation and control of cell substrate

[redacted]. A master cell bank (MCB) was prepared from the seed bank for process development, and a working cell bank (WCB) was prepared from the MCB.

The results of characterization (isoenzyme analysis, copy number, plasmid sequence, Southern blotting) of the MCB and post-production cell bank (PPCB) showed genetic stability over the production period.

In addition, purity tests (mycoplasma testing, sterility test, antibody production test, *in vivo* virus testing, *in vitro* virus testing, electron microscopy, reverse transcriptase and infectivity assays, *in vitro* bovine virus test, *in vitro* porcine virus test) were performed on the MCB and PPCB, and a part of purity tests were performed on the WCB. As a result, no adventitious viruses or nonviral infectious agents were detected for the parameters tested, except endogenous retroviruses and retrovirus-like particles commonly found in rodent-derived cell lines.

Appropriate storage conditions have been set for the MCB and WCB. [redacted].

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

[redacted].

Process evaluation at a laboratory or commercial scale has been conducted for the manufacturing process for cAC10.

2.A.(1).1).iii) Safety evaluation of adventitious infectious substances

No biological ingredients other than CHO cells, recipient cell line, are used in the manufacturing process for cAC10. [redacted].

Purity tests have been performed on the MCB, WCB, and PPCB [see "2.A.(1).1).i) Preparation and control of cell substrate"]. In addition, bacterial endotoxin test, sterility test, mycoplasma testing (culture method, DNA staining method), transmission electron microscopy, adventitious virus test (*in vitro*), and quantitative polymerase chain reaction (PCR) assay (murine minute virus [MMV] assay) were performed on the pre-harvest unprocessed bulk at a commercial scale. As a result, no contamination by viral or nonviral infectious agents was detected within the range of the performed tests. In addition, mycoplasma testing, adventitious virus test (*in vitro*), and

MMV assay (quantitative PCR method) on the unprocessed bulk have been defined as in-process control tests.

For the purification processes, viral clearance was evaluated by using model viruses; the results demonstrated the processes have a certain level of capacity to remove viruses.

Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	MMV	Pseudorabies virus	Reovirus type 3
Chromatographic process 1	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≥[redacted]	[redacted]	≥[redacted]	[redacted]
Chromatographic process 2	[redacted]	—*	—*	—*
Chromatographic process 3	[redacted]	[redacted]	[redacted]	≥[redacted]
[redacted]	≥[redacted]	≥[redacted]	≥[redacted]	≥[redacted]
Overall virus reduction factor	≥16.8	≥7.7	≥14.5	≥11.1

* Total log reduction ≤[redacted]

2.A.(1).1).iv) Characterization

(a) Structure/Composition

a) Primary structure

- Amino acid composition analysis established that the amino acid composition is consistent with that expected from the base sequence.

- [redacted].

b) Higher order structure

- [redacted].

- Free sulfhydryl analysis under denaturing and non-denaturing conditions showed [redacted] and [redacted] of free sulfhydryl groups per 1 mol of cAC10, respectively.

- Fourier-transform infrared spectroscopy (FTIR) and far-ultraviolet circular dichroism (CD) spectrometry showed that the main secondary structure element of cAC10 is the β-sheet.

- Differential scanning calorimetry (DSC) showed two thermal transition temperatures of [redacted]°C and [redacted]°C.

c) Carbohydrate structure

- [redacted].

- [redacted]

[redacted].

- [redacted].

d) Physicochemical properties

Molecular weight

- [redacted].

Electrophoresis

- [redacted]. Under reducing conditions, besides major bands corresponding to the heavy and light chains, minor bands were observed at approximately [redacted] kDa and [redacted] kDa.

- CE-SDS under non-reducing conditions demonstrated fragment peaks in addition to the main peak of the monomer. [redacted].

- Imaged capillary isoelectric focusing system (icIEF) showed the isoelectric point of [redacted] for the main peak, and demonstrated the presence of acidic and basic variants represented by acidic and basic peaks, respectively.

Liquid chromatography

- [redacted].

- [redacted].

Other properties

- Absorption coefficient (at 280 nm) was [redacted] ± [redacted] mL/(mg·cm).

e) Biological properties

- [redacted].

- The equilibrium dissociation constant (K_D) for CD30 antigen based on surface plasmon resonance (SPR) was [redacted] nmol/L.

- [redacted].
- [redacted].

f) Product-related substances

No molecular species were identified as product-related substances.

(b) Impurities

a) Process-related impurities

[redacted]. All process-related impurities have been confirmed to be adequately removed through the manufacturing process. HCP content is controlled by specifications for cAC10.

b) Product-related impurities

[redacted]. Product-related impurities are controlled by specifications for cAC10, the drug substance, and drug product.

2.A.(1).1).v) Control

[redacted].

2.A.(1).2) MMAE-linker conjugate (SGD-1006)

2.A.(1).2).i) Characterization

SGD-1006 is a white to yellow powder and has been characterized by description, solubility, dissolution temperature range, and optical rotation.

The chemical structure of SGD-1006 has been elucidated by elementary analysis, nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), mass spectrometry (MS), and infrared spectrophotometry.

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

[redacted].

[redacted]. In addition, products of all steps are controlled as critical intermediates in order to ensure consistent quality of SGD-1006.

products of all steps

2.A.(1).2).iii) Control of SGD-1006

The proposed specifications for SGD-1006 include content, description, identification (FTIR, HPLC), optical rotation, purity (main peak, related substances [HPLC]; residual solvents [gas chromatography (GC)]); residual metal 1 [mass spectrometry]), water content, and assay (HPLC).

2.A.(1).3) Brentuximab vedotin (genetical recombination)

2.A.(1).3).i) Manufacturing process

[redacted].

The manufacturing process of the drug substance was evaluated on a commercial scale.

2.A.(1).3).ii) Manufacturing process development (Comparability)

Major changes in the manufacturing process made during the drug substance development are as shown below (each manufacturing process is denoted as Manufacturing processes A, B, C [for clinical studies], and C [for process validation]). On the occasion of change from Manufacturing process B to C (for clinical studies), the manufacturing process of the drug product was also changed [see "2.A.(2).3) Manufacturing process development (Comparability)"].

- [redacted]
- [redacted]
- [redacted]

The comparability of the quality attributes of the drug substance was evaluated at the time of making these changes to the manufacturing process, which demonstrated the comparability between pre-change and post-change batches of the drug substance.

2.A.(1).3).iii) Characterization

(a) Structure and composition

a) Primary structure

- Amino acid composition analysis showed a decrease in cysteine content, which was considered due to binding with SGD-1006, but demonstrated that the amino acid composition is consistent with the composition expected from the base sequence.
- [redacted].

b) Higher order structure

- [redacted].

- FTIR and far-ultraviolet CD spectral analyses showed that, like that of cAC10, the main secondary structure element of brentuximab vedotin is the β-sheet.

- Results from DSC showed thermal transition temperatures of [redacted] °C and [redacted] °C, which are the same as those of cAC10. [redacted].

c) Carbohydrate structure

- [redacted].

d) Drug load variants

- [redacted]. The molar ratio (MR) of conjugated drug to antibody was distributed in the range from [redacted] to [redacted] (MR variants), and the average MR (MR_D) for the reference material produced by Manufacturing process C was 4.0.

- [redacted].

- [redacted].

e) Physicochemical properties

Molecular weight

- [redacted].

Electrophoresis

- [redacted].

- Results from icIEF showed isoelectric point of the major variant at [redacted] and a profile similar to that of cAC10.

Liquid chromatography

- [redacted].

Other properties

- The absorption coefficient (at 280 nm) was [redacted] ± [redacted] mL/(mg·cm), which was similar to that of cAC10.

f) Biological properties

- [redacted].

- [redacted].
- [redacted].
- [redacted].
- [redacted].
- [redacted].
- Little ADCC activity against L428 and L540cy cell lines was detected in the presence of effector cells (natural killer cells), as in the case of cAC10. Also, no CDC activity against the WIL2-S cell line was detected, as in the case of cAC10.

g) Product-related substances

No molecular species were identified as product-related substances.

(b) Impurities

a) Process-related impurities

[redacted]. The applicant explained that all process-related impurities are adequately removed through the manufacturing process or acceptable based on the results of safety evaluation. [redacted].

b) Product-related impurities

[redacted]. Product-related impurities are controlled by the specifications for the critical intermediates (cAC10, SGD-1006), drug substance, and drug product.

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

[redacted].

2.A.(1).3).v) Stability of drug substance

The major stability studies of the drug substance are as shown in the table below.

Outline of major stability studies of drug substance

		Number of batches	Storage conditions	Study period	Storage configuration
Long-term testing		Manufacturing process A: 3	≤ °C	months	
		Manufacturing process C (for clinical studies): 3		months*	
		Manufacturing process C (for process validation): 3		months*	
Accelerated testing		Manufacturing process C (for clinical studies): 3	± °C	months*	
Stress testing	High temperature	Manufacturing process C (for clinical studies): 3	± °C	weeks	
			± °C, ± %RH	weeks	
			± °C, ± %RH	weeks	
	Light	Manufacturing process C (for clinical studies): 1	Integrated illumination of 1.2 million lux·h and integrated near ultraviolet energy of 200 W·h/m^2		

* Stability study is ongoing.

Neither the long-term testing nor the accelerated testing showed significant changes in quality attributes throughout the study period.

. The long-term testing for drug substance batches manufactured by Manufacturing process C (for clinical studies) and Manufacturing process C (for process validation) will be continued up to months.

2.A.(2) Drug product

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

The drug product is an injectable formulation containing 55 mg of the drug substance per vial (30 mL). The drug product contains citric acid hydrate, sodium citrate hydrate, trehalose hydrate, and polysorbate 80 as excipients. Each vial contains an overfill of 10% of the labeled amount of the drug substance so that 10 mL of injection solution containing 50 mg of the drug substance can be withdrawn when the drug product is reconstituted with 10.5 mL of water for injection. The secondary packaging is a carton.

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

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The manufacturing process of the drug product was evaluated on a commercial scale.

A QbD approach has been utilized for development of the drug product [see "2.A.(4) Quality by design (QbD)"].

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

[redacted]. The manufacturing process of the drug product under development is denoted as Manufacturing processes A, B, and C in accordance with the manufacturing process of the drug substance.

The comparability of the quality attributes of the drug product was evaluated at the time of making these changes to the manufacturing process, which demonstrated the comparability between pre-change and post-change batches of the drug product.

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

[redacted].

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

The major stability studies of the drug product are as shown in the table below.

Outline of major stability studies of drug product

		Number of batches	Storage conditions	Study period	Storage configuration
Long-term testing		Manufacturing process A: 3	5 ± 3°C	[redacted] months*1	Glass vial
		Manufacturing process C: 3		[redacted] months*2	
Accelerated testing		Manufacturing process C: 3	25 ± 2°C, 60 ± 5% RH	[redacted] months*2	
Stress testing	High temperature	Manufacturing process C: 3	[redacted] ± [redacted]°C, [redacted] ± [redacted]% RH	[redacted] months	
		Manufacturing process C: 3	[redacted] ± [redacted]°C, [redacted] ± [redacted]% RH	[redacted] months	
		Manufacturing process C: 3	[redacted]°C ± [redacted]°C	[redacted] weeks	
	Light	Manufacturing process C: 1	Integrated illumination of 1.2 million lux·h and integrated near ultraviolet energy of 200 W·h/m^2		Glass vials and glass vials light-shielded with carton

*1, [redacted] months for [redacted] batches, and [redacted] months for the other [redacted] batches; *2, Stability study is ongoing.

Neither the long-term testing nor the accelerated testing showed significant changes in quality attributes throughout the study period.

[redacted].

[redacted].

Based on the above results of the stability studies, the applicant proposed a shelf life of 36 months for the drug product when stored at 2°C to 8°C in glass vials protected from light [see "2.B.(3) Shelf life for the drug product"]. The long-term testing of drug product batches manufactured by Manufacturing process C will be continued up to [redacted] months.

2.A.(3) Reference material

The reference material is prepared from the drug substance and stored at ≤[redacted]°C. At present, the reference material has been confirmed to be stable up to [redacted] months. [redacted].

2.A.(4) Quality by design (QbD)

The quality by design (QbD) approach has been utilized for development of brentuximab vedotin. Among quality attributes of brentuximab vedotin, the followings were identified as critical quality attributes (CQAs) from general knowledge etc., and to-be-controlled steps and control methods for each CQA were determined based on an assessment of processes which may affect each of the CQAs and the degree of impact. In addition, critical process parameters (CPPs) identified by manufacturing process characterization were incorporated into the process control. Based on these, control strategies to ensure the quality of brentuximab vedotin were developed.

- [redacted].

2.B Outline of the review by PMDA

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

2.B.(1) Identification and control of CQAs

[redacted].

- [redacted]
- [redacted]

PMDA considers as follows:

[redacted]. Therefore, PMDA considers that the applicant's approach described above is not necessarily appropriate in terms of identification of CQAs of

brentuximab vedotin, but that its quality attributes are appropriately controlled through specifications and in-process controls, etc.

2.B.(2) Acceptance criteria for free impurity (Impurity A) of drug substance

The applicant set out the acceptance criterion for Impurity A, a free drug-related impurity, as "Content ≤ %." [redacted] Also, the free drug-related impurity can be controlled at a lower level in light of the batch analysis, which demonstrated that the levels of this impurity were constantly kept at around %. Therefore, PMDA asked the applicant to explain the appropriateness of the acceptance criterion for this free drug-related impurity.

* [redacted]

The applicant responded as follows:

[redacted]. In addition, the maximum tolerated dose (MTD) of MMAE is 580 μg/kg (for monkeys, once every 3 weeks for 4 doses in total) [see "3.(iii).A.(2).2) Eleven-week repeated intravenous dose toxicity study in cynomolgus monkeys"], which corresponds to the human dose (one-tenth of the human equivalent dose) of μg/kg, higher than the amount of Impurity A to be administered (μg/kg). Based on the above, the acceptance criterion for Impurity A is considered acceptable in terms of safety and appropriate based on the maximum amount of Impurity A to be administered and the MTD of MMAE.

Although the content of Impurity A in batches of the drug substance ranged from % to % and controlled below a level requiring a specific acceptance criterion, a specific acceptance criterion has been developed for Impurity A because a probability of its presence is high due to the manufacturing process characteristics. Contents of Impurity A and other free drug-related impurities will be continuously confirmed by release testing, stability studies, and annual quality reviews. While at present sufficient data have not been collected to develop an acceptance criterion for Impurity A based on manufacturing experience, consideration will be given to whether to reestablish the acceptance criterion once manufacturing data from adequate number of batches have been collected.

Based on the facts that no safety problems have been found with the proposed acceptance criterion for Impurity A and that the contents of Impurity A and other free drug-related impurities will be continuously monitored in the future, PMDA concluded that the applicant's control strategy for free drug-related impurities including Impurity A is acceptable.

2.B.(3) Shelf life for the drug product

[redacted].

PMDA instructed the applicant to establish a shelf life of the drug product based on the long-term stability data on the formulation manufactured by Manufacturing process C. The applicant additionally submitted long-term stability data up to 36 months on 3 batches of the formulation manufactured by Manufacturing process C, and responded that a shelf life of 36 months has been proposed for the drug product when stored at 2°C to 8°C in glass vials protected from light because no significant change was observed in any of the test attributes throughout the study period.

PMDA accepted the applicant's response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Growth inhibitory effect on cells derived from CD30-positive Hodgkin's lymphoma (HL) and anaplastic large-cell lymphoma (ALCL) (Reports [redacted]-1363-A, [redacted]-1304, [redacted]-1308, [redacted]-1305)

In vitro:

The growth inhibitory effect of brentuximab vedotin was investigated by the flow cytometry (FCM) method using cell lines derived from human Hodgkin's lymphoma (HL) (L540cy and L428 cell lines) and human anaplastic large-cell lymphoma (ALCL) (Karpas 299, SR-786, and SU-DHL-1 cell lines) that were determined as CD30-positive. As a result, the IC_{50} value of brentuximab vedotin for each of these cell lines was as shown in the table below. The CD30-negative WSU-NHL cell line derived from human non-Hodgkin's lymphoma (NHL), HCT-116 cell line derived from human colon cancer, and monomethyl auristatin E (MMAE) with an inhibitory effect on tubulin polymerization, which is a component of brentuximab vedotin, an antibody-drug conjugate (ADC), were used as controls.

Growth inhibitory effect of brentuximab vedotin and MMAE

Cell line	IC_{50} value (nmol/L)	
	Brentuximab vedotin	MMAE
L540cy	0.091 ± 0.031	0.639 ± 0.109
L428	>6.7	1.579 ± 0.151
Karpas 299	0.032 ± 0.005	0.334 ± 0.072
SR-786	0.008 ± 0.005	0.111 ± 0.035
SU-DHL-1	0.062 ± 0.043	0.537 ± 0.279
WSU-NHL	>6.7	0.234 ± 0.101
HCT-116	>6.7	2.255 ± 0.456

Mean ± standard deviation (SD), n = 3

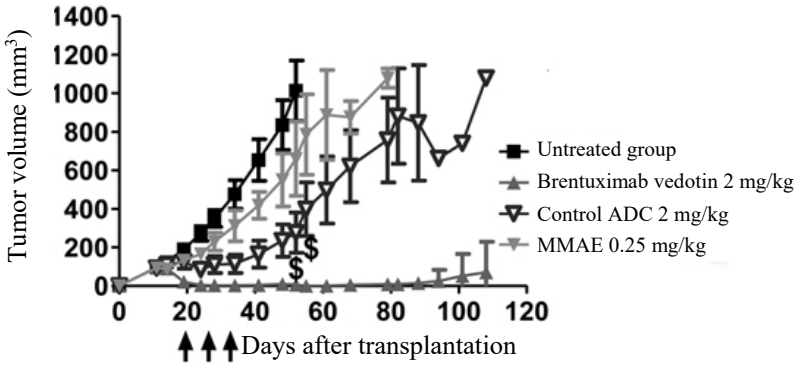
***In vivo*:**

(a) L428 Cell line

NOD/SCID/γc^{null} mice were generated by backcross matings of non-obese disease (NOD) mice with severe combined immunodeficient (SCID) mice and interleukin-2 (IL-2) receptor γ chain (common to cytokine receptors) deficient (γc^{null}) mice. The NOD/SCID/γc^{null} mice underwent a subcutaneous transplant of the L428 cell line and were subjected to the test for the tumor growth-inhibitory effect of brentuximab vedotin. Starting 10 days after transplantation when the mean volume of transplanted tumor reached approximately 100 mm^3, 1 mg/kg of brentuximab vedotin was intraperitoneally administered once every 4 days for 4 doses in total, and the tumor volume was calculated (1 mg/kg of ADC that does not bind to human CD30 [control ADC] was intraperitoneally administered once every 4 days for 4 doses in total as a control). As a result, a

statistically significant growth inhibitory effect was observed in the brentuximab vedotin group compared with the untreated and control ADC groups.

In addition, a study similar to the above was conducted using an increased dose level (2 mg/kg) of brentuximab vedotin and the control ADC for 3 doses in total. The results showed a statistically significant growth inhibitory effect in the brentuximab vedotin and control ADC groups compared with the untreated group [the figure below].



Growth inhibitory effect of brentuximab vedotin (L428 cell line)

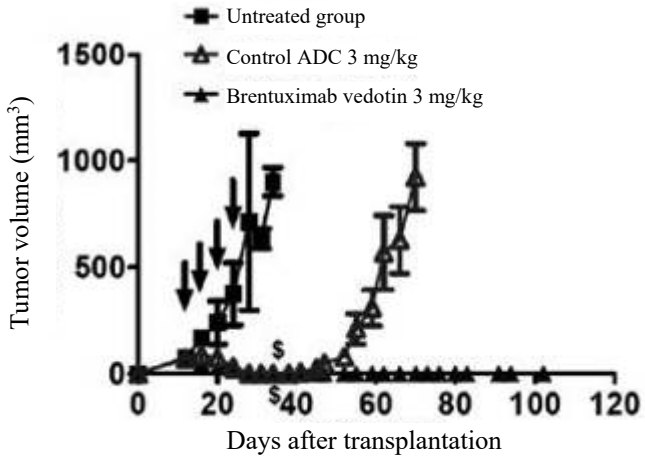
Mean ± SD; n = 5 (number of animals at the initiation of dosing [1, 2, and 1 animals in the control ADC group were euthanized on Days 73, 82, and 88, respectively, and 1 and 2 animals in the MMAE group on Days 55 and 61, respectively, because the tumor volume exceeded 1000 mm^3]); each arrow indicates the day of administration of brentuximab vedotin, control ADC, or MMAE; $, $P < 0.001$ (t-test) against the untreated group (the statistical analysis was performed on the tumor volume 52 days after tumor transplantation.)

The applicant explained that although the reason why L428 cell line had been insensitive *in vitro* but sensitive *in vivo* to brentuximab vedotin was unclear, mechanisms including intracellular uptake of brentuximab vedotin may differ between *in vitro* and *in vivo* and its sensitivity *in vivo* may be observed by mechanisms such as phagocytosis.

(b) L540cy cell line

The growth inhibitory effect of brentuximab vedotin was investigated using SCID mice transplanted subcutaneously with L540cy cell line. Starting 12 days after transplantation when the mean volume of transplanted tumor reached approximately 100 mm^3, 1 mg/kg of brentuximab vedotin was administered intraperitoneally once every 4 days for 4 doses in total, and the tumor volume was calculated (1 mg/kg of control ADC was administered intraperitoneally once every 4 days for 4 doses in total as a control). As a result, a statistically significant growth inhibitory effect was observed in the brentuximab vedotin group compared with the untreated and control ADC groups.

In addition, a study similar to the above was conducted using an increased dose level (3 mg/kg) of brentuximab vedotin and control ADC. The results showed a statistically significant growth inhibitory effect in the brentuximab vedotin and control ADC groups compared with the untreated group [the figure below].



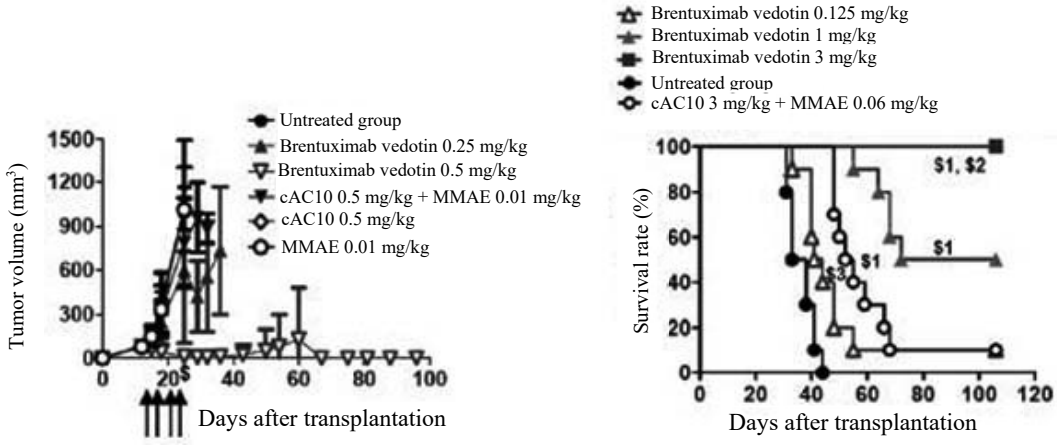
Growth inhibitory effect of brentuximab vedotin (L540cy cell line)

Mean ± SD; n = 5 (number of animals at the initiation of dosing [1 animal in the control ADC group was euthanized on Day 62 because the tumor volume exceeded 1000 mm^3]); each arrow indicates the day of administration of brentuximab vedotin or control ADC; $, $P < 0.001$ (t-test) against the untreated group (the statistical analysis was performed on the tumor volume 34 days after tumor transplantation.)

(c) Karpas 299 cell line

The growth inhibitory effect of brentuximab vedotin was investigated using SCID mice transplanted subcutaneously with Karpas 299 cell line. Brentuximab vedotin at doses of 0.25 and 0.5 mg/kg was administered intravenously once every 4 days for 4 doses in total, and the tumor volume was calculated (0.5 mg/kg of chimeric monoclonal antibody [cAC10], consisting of variable regions of mouse anti-human CD30 antibody and constant regions of human immunoglobulin G1 [IgG1], 0.01 mg/kg of MMAE, or a mixture of cAC10 0.5 mg/kg and MMAE 0.01 mg/kg was administered intravenously once every 4 days for 4 doses in total as controls). As a result, a statistically significant growth inhibitory effect was observed in the brentuximab vedotin 0.5 mg/kg group compared with the untreated group [left panel of the figure below].

In addition, effects of brentuximab vedotin on survival time were investigated using SCID mice with Karpas 299 cell line injected through tail-vein. Starting 9 days after transplantation, brentuximab vedotin at doses of 0.125, 1, or 3 mg/kg was administered intravenously once every 4 days for 4 doses in total, and the survival rate was calculated (a mixture of cAC10 3 mg/kg of and MMAE 0.06 mg/kg was administered intravenously once every 4 days for 4 doses in total as a control). As a result, a statistically significant increase in survival time was observed in all groups compared with the untreated group [right panel of the figure below].



Growth inhibitory effect and survival-extending effects of brentuximab vedotin (Karpas 299 cell line)

Mean ± SD

Left panel: n = 8 (number of animals at the initiation of dosing [3 and 1 animals in the brentuximab vedotin 0.25 mg/kg group were euthanized on Days 25 and 32, respectively, 1 animal in the brentuximab vedotin 0.5 mg/kg group on Day 60, and 2, 3, and 2 animals in the cAC10 + MMAE group on Days 25, 29, and 32, respectively, because the tumor volume exceeded 1000 mm^3]); each arrow indicates the day of administration of brentuximab vedotin, cAC10, MMAE, or mixture of cAC10 and MMAE; $, $P < 0.001$ (t-test) against the untreated group (the statistical analysis was performed on the tumor volume at 25 days after tumor transplantation).

Right panel: n = 10 (number of animals at the initiation of dosing); $1, $P < 0.001$ against the untreated group; $2, $P < 0.001$ against the cAC10 + MMAE group; $3, $P < 0.01$ against the untreated group (log-rank test) (the statistical analysis was performed on the survival time).

The applicant explained that the growth inhibitory effect of brentuximab vedotin against CD30-positive HL and ALCL was demonstrated by the results from the above *in vitro* and *in vivo* studies.

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

i) Binding characteristics to CD30-positive cells and recombinant CD30 proteins (Reports [redacted]-0411-B, [redacted]-1356, [redacted]-0922, [redacted]-1355, [redacted]-1435, [redacted]1299, 01-130)

Binding activities of brentuximab vedotin and cAC10 to CD30 were investigated by time-resolved fluorescence assay in Karpas 299 cell line. As a result, the dissociation constant (K_D value ± standard error [SE] of the mean) was 2.48 ± 0.38, 2.48 ± 0.45, and 1.81 ± 0.37 for brentuximab vedotin (3 batches) and 1.49 ± 0.08 nmol/L for cAC10, indicating binding activities similar to CD30 between brentuximab vedotin and cAC10.

In addition, binding activities of brentuximab vedotin and cAC10 to CD30 were investigated by the FCM method using CD30-positive lymphocytes from humans, cynomolgus monkeys, rats, and mice. As a result, binding activities of both brentuximab vedotin and cAC10 to CD30 were similar between humans and cynomolgus monkeys. However, binding activity of brentuximab vedotin to CD30-positive lymphocytes from rats and mice was not detected.

[redacted].

ii) Intracellular uptake and lysosomal trafficking of brentuximab vedotin (Report [redacted]-1309)

Intracellular localization of brentuximab vedotin was investigated in L540cy cell line by immunofluorescence staining assay with fluorescently labeled IgG antibodies. As a result, its lysosomal localization was confirmed, as evidenced by the same staining pattern between lysosomes, which are stained by anti-lysosome-associated membrane protein 1 (anti-Lamp-1), and both brentuximab vedotin and brentuximab vedotin-derived cAC10.

iii) Release of MMAE (Reports [redacted]-1361, [redacted]-1861, [redacted]-0446-B)

A study on release of MMAE from brentuximab vedotin was performed using Western blotting and mass spectrometry by incubating brentuximab vedotin with either purified human cathepsin B (one type of lysosomal proteases) or lysosomal fraction prepared from Karpas 299 cell line. As a result, release of MMAE from brentuximab vedotin was confirmed.

In addition, changes in concentrations of cell-surface-bound brentuximab vedotin, internalized brentuximab vedotin (bound form), and free MMAE over time were investigated in L540cy or Karpas 299 cell line by liquid scintillation counting of brentuximab vedotin containing ^{14}C-MMAE. As a result, brentuximab vedotin was found to mostly bind to cell membranes. Subsequently, a time-dependent increase was observed in the intracellular concentration of ^{14}C-MMAE, which was mostly in the free form.

iv) Effects on microtubule growth (Reports [redacted]-1357, [redacted]1306)

Effects of MMAE on microtubule growth rate were investigated by spectrophotometry using tubulin purified from bovine brain. As a result, the growth rate of microtubule treated with MMAE was found to be similar to that of microtubule treated with vinblastine sulfate (vinblastine), a tubulin polymerization inhibitor.

In addition, effects of brentuximab vedotin on microtubule growth were investigated by immunofluorescence staining assay using embryonal carcinoma-derived Tera-2 cell line, representing CD30-positive adherent cells. As a result, a decrease in cell count as well as cell rounding and blurring of microtubule staining (detected by biotinylated anti-tubulin antibody and fluorescently labeled streptavidin) were observed as compared with the untreated group.

v) Cell-cycle arrest- and apoptosis-inducing effects (Report [redacted]-1307)

Cell-cycle arrest- and apoptosis-inducing effects of brentuximab vedotin were investigated in L540cy and Karpas 299 cell lines based on cell counts in G2/M and sub-G0/G1 phases. As a result, an increase in cell counts in G2/M and sub-G0/G1 phases was observed after 30 hour-treatment with brentuximab vedotin or MMAE. In NHL-derived CD30-negative Ramos cell line, an increase in cell counts in G2/M and sub-G0/G1 phases was observed after MMAE treatment, but cell counts in G2/M and sub-G0/G1 phases did not change after treatment with brentuximab vedotin.

vi) Phagocytosis-inducing effect (Report [redacted]-1329)

A study on the macrophage phagocytosis-inducing effect of brentuximab vedotin was performed by the FCM method using macrophages isolated from human peripheral-blood mononuclear cells and human lymphoblast-derived WIL2-S cell line expressing CD30. As a result, macrophages phagocytosed at least 70% of WIL2-S cells binding to brentuximab vedotin, but phagocytosed 20% or less of WIL2-S cells not binding to brentuximab vedotin. Brentuximab vedotin did not induce phagocytosis by macrophages of CD30-negative Ramos cell line.

Based on the above results, the applicant explained that involvement of phagocytosis by macrophages in the growth inhibitory effect of brentuximab vedotin is unknown because studies in mice transplanted with a human malignant tumor-derived cell line cannot differentiate between

phagocytosis by macrophages and direct cytotoxicity of brentuximab vedotin although brentuximab vedotin was suggested to induce phagocytosis of CD30-positive cells by macrophages.

vii) Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities (Report [redacted]-1329)

Antibody-dependent cell-mediated cytotoxicity (ADCC) activity of brentuximab vedotin was little observed against L428 and L540cy cell lines in the presence of effector cells (natural killer cells). In addition, no complement-dependent cytotoxicity (CDC) activity of brentuximab vedotin was observed against WIL2-S cell line in the presence of human serum.

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

3.(i).A.(2).1) Effects on central nervous, cardiovascular, and respiratory systems (Report [redacted]00051)

The effects of brentuximab vedotin (0.3, 1, 3 mg/kg) on (a) central nervous system (general symptoms, neurological findings, body temperature), (b) cardiovascular system (electrocardiogram, heart rate, blood pressure [systolic and diastolic blood pressures, mean arterial pressure]), (c) respiratory system (respiratory rate, blood gases), and (d) others (body weight, food consumption, plasma biochemistry) were investigated in a single-dose study in cynomolgus monkeys (3 males/group). As a result, brentuximab vedotin was not found to affect the test parameters (a) to (d) above.

3.(i).A.(2).2) Effects on hERG current (Report 129-09-001)

A study on the effects of MMAE (10, 100 μmol/L) on human ether-a-go-go related gene (hERG) potassium current was performed by the patch-clamp method using human embryonic kidney-derived HEK-293 cell line transfected with hERG. MMAE at 100 μmol/L inhibited the current by 23.7% ± 5.6% (mean ± SE) (n = 4), with a significant difference compared with the control (saline) group ($P < 0.05$, t-test). However, MMAE at 10 μmol/L inhibited the current by 10.3% ± 3.0% (mean ± SE) (n = 4), without a significant difference compared with the control (saline) group. The applicant explained that brentuximab vedotin-derived MMAE is unlikely to block hERG potassium channels because an MMAE concentration of 10 μmol/L is ≥1000-fold the mean C_{max}* of MMAE in plasma after administration of 1.8 mg/kg of brentuximab vedotin.

* C_{max} of MMAE after the first dose of brentuximab vedotin (1.8 mg/kg) was 5.00 nmol/L in Study TB-BC010088.

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

Based on the submitted data and the following reviews, PMDA concluded that the brentuximab vedotin is expected to be effective against CD30-positive HL and ALCL.

Mechanism of action of brentuximab vedotin

The applicant explained the mechanism of action of brentuximab vedotin as follows:
Brentuximab vedotin selectively binds to CD30 expressed on the cell membrane of HL and ALCL cells. After internalization in the form of a conjugate with CD30, brentuximab vedotin is trafficked to lysosomes, where MMAE is released by the action of proteases. The released MMAE inhibits tubule polymerization and microtubule formation by binding to tubulin, resulting in induction of cell cycle arrest and apoptosis [see "3.(i).A.(1).2) Mechanism of action"].

Since brentuximab vedotin is a drug to be used in patients with HL or ALCL who have previously been treated with a vinca alkaloid antineoplastic drug (vinblastine or vincristine sulfate), which is a tubulin polymerization inhibitor, as with brentuximab vedotin [see "4.(iii).B.(4) Clinical positioning"], PMDA asked the applicant to explain the efficacy of brentuximab vedotin in these patients.

The applicant responded as follows:
The reported mechanisms of resistance to vinca alkaloid antineoplastic drugs include (a) structural change in microtubules, (b) stimulation of drug metabolizing systems, and (c) activation of drug efflux mechanism such as P-glycoprotein (P-gp) (*J Clin Oncol*. 1999;17:1061-70).

MMAE binding site on tubulin is considered different from vinca alkaloid antineoplastic drug binding site based on the fact that Dolastatin 10, an MMAE analog, does not competitively inhibit the binding of vinca alkaloid antineoplastic drugs to tubulin (*J Biol Chem*. 2004;279:30731-40, *J Biol Chem*. 1990;265:17141-9). Thus, brentuximab vedotin is presumed to have a binding ability to tubulin also in patients who acquired resistance to vinca alkaloid antineoplastic drugs through the mechanism (a) described above.

Taking account of the above etc., brentuximab vedotin is considered to be effective also in patients with HL or ALCL who have previously been treated with vinca alkaloid antineoplastic drugs.

PMDA accepted the applicant's response.

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics (PK) of brentuximab vedotin in animals has been studied in rats and monkeys. Pharmacokinetic studies (e.g., plasma protein binding, drug-metabolizing enzyme, transporters) related to MMAE, a component of brentuximab vedotin, have been performed using biomaterials from humans or other animals.

3.(ii).A.(1) Analytical methods

3.(ii).A.(1).1) Assay method for brentuximab vedotin

[redacted].

3.(ii).A.(1).2) Assay method for total antibody (TAb)

[redacted].

* Defined as MMAE-conjugated cAC10 and free cAC10. Neither the half-life ($t_{1/2}$) nor PK parameters related to $t_{1/2}$ ($AUC_{0-\infty}$, CL, V_{ss}) intrinsic to TAb were evaluated because ELISA measurements derive from multiple molecular species, each having individual clearance rates, including brentuximab vedotin and cAC10.

3.(ii).A.(1).3) Assay method for MMAE

MMAE in rat and monkey serum and in rat amniotic fluid was assayed by the LC-MS/MS method.

3.(ii).A.(1).4) Assay method for rat anti-human antibody (RAHA) and primate anti-human antibody (PAHA)

[redacted]

[redacted].

3.(ii).A.(2) Absorption

3.(ii).A.(2).1) Single-dose administration

A single intravenous dose of 0.5 or 5.0 mg/kg of brentuximab vedotin was administered to female rats, and serum concentrations of brentuximab vedotin and TAb were determined [the table below]. The expression of RAHA was observed in 3 of 12 rats (25%, all in the 5.0 mg/kg group) after administration of brentuximab vedotin. Brentuximab vedotin and TAb were eliminated in a multiphasic manner after administration of brentuximab vedotin. In addition, C_{max} and AUC of brentuximab vedotin and TAb increased generally in a dose-proportional manner. No clear differences were observed in PK parameters of brentuximab vedotin and TAb between RAHA-positive and RAHA-negative rats.

PK parameters of brentuximab vedotin and TAb after single intravenous administration of brentuximab vedotin to female rats

	Dose (mg/kg)	n*	RAHA	C_{max} (μg/mL)	T_{max} (day)	$AUC_{0\text{-last}}$ (day·μg/mL)	$AUC_{0\text{-}\infty}$ (day·μg/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Brentuximab vedotin	0.5	6	Negative	13	0.042	20	20	14.6	25	183
	5.0	3	Negative	171	0.042	253	253	8.5	20	135
	5.0	3	Positive	171	0.042	245	246	10.1	20	152
TAb	0.5	6	Negative	15	0.042	40	-	-	-	-
	5.0	3	Negative	240	0.042	557	-	-	-	-
	5.0	3	Positive	240	0.042	475	-	-	-	-

Arithmetic means; *, Blood samples were collected from different rats at each time point.

A single intravenous dose of 3 or 10 mg/kg of brentuximab vedotin was administered to female rats, and serum concentrations of MMAE were determined [the table below]. C_{max} and AUC of MMAE increased generally in a dose-proportional manner. The applicant explained that MMAE was suggested to be slowly released from brentuximab vedotin as evidenced by the median T_{max} of MMAE (1.0 day).

PK parameters of MMAE after single intravenous administration of brentuximab vedotin to female rats

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (day)	$AUC_{0\text{-last}}$ (day·ng/mL)	$AUC_{0\text{-}\infty}$ (day·ng/mL)	$t_{1/2}$ (day)
3	0.34	1.0	0.94	1.2	2.2
10	0.93	1.0	3.6	3.9	2.5

Arithmetic means, 3 animals/time point (blood samples were collected from different rats at each time point.)

Following single intravenous administration of brentuximab vedotin 0.3 or 1.0 mg/kg over 1 hour or single intravenous administration of brentuximab vedotin 3 mg/kg over 30 minutes to female cynomolgus monkeys, serum concentrations of brentuximab vedotin, TAb, and MMAE were determined [the table below]. PAHA was tested by ELISA, and 17 of 18 animals (94%) were positive for PAHA after administration of brentuximab vedotin. Although no rigorous analyses have been conducted on the effect of PAHA on PK of brentuximab vedotin and TAb, serum concentrations of brentuximab vedotin and TAb decreased rapidly during the terminal phase in PAHA-positive animals compared with PAHA-negative animals. The applicant explained that PAHA expression was considered to be one possible factor for the rapid decrease.

The increase in $AUC_{0\text{-}\infty}$ of brentuximab vedotin was generally greater than dose-proportional within the dose range from 0.3 to 3 mg/kg. The applicant explained that the antigen-dependent and antigen-independent eliminations were involved in the elimination of brentuximab vedotin,

and that high-dose administration of brentuximab vedotin may have saturated the antigen-dependent elimination. CL and V_{ss} of brentuximab vedotin were similar, irrespective of the dose administered. In addition, $AUC_{0\text{-last}}$ of TAb and C_{max} of MMAE after administration of brentuximab vedotin increased generally in a dose-proportional manner within the dose range from 0.3 to 3 mg/kg.

PK parameters of brentuximab vedotin and TAb after single intravenous administration of brentuximab vedotin to female cynomolgus monkeys

	Dose (mg/kg)	n	PAHA	C_{max} (μg/mL)	T_{max} *1 (day)	$AUC_{0\text{-last}}$ (day·μg/mL)	$AUC_{0\text{-}\infty}$ (day·μg/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Study 8201-470										
Brentuximab vedotin	0.3	6	Positive	6.95 ± 1.25	0.0486	10.7 ± 1.8	11.0 ± 1.7	1.82 ± 0.37	27.7 ± 4.3	68.0 ± 11.8
	1	5*2	Positive	29.2 ± 5.5	0.0486	53.3 ± 8.3	55.3 ± 9.2	2.69 ± 0.56	18.5 ± 3.0	67.4 ± 19.8
TAb	0.3	6	Positive	8.30 ± 1.77	0.0486	17.4 ± 2.0	-	-	-	-
	1	6	Positive	24.8 ± 2.8	0.0486	68.6 ± 7.5	-	-	-	-
Study 8213480										
Brentuximab vedotin	3	5	Positive	77.20 ± 9.87	0.0278	140.27 ± 20.28	140.41 ± 20.29	1.61 ± 0.24	21.70 ± 2.89	63.28 ± 8.58
	3	1	Negative	89.16	0.0278	209.98	210.09	2.44	14.28	57.77
TAb	3	5	Positive	87.41 ± 7.30	0.0278	227.94 ± 23.91	-	-	-	-
	3	1	Negative	96.62	0.0278	392.39	-	-	-	-

Arithmetic means ± SD; *1, Median; *2, One animal determined as an outlier by Dixon test was excluded.

PK parameters of MMAE after single intravenous administration of brentuximab vedotin to female cynomolgus monkeys

Dose of brentuximab vedotin (mg/kg)	n	PAHA	C_{max} (ng/mL)	T_{max}* (day)	$AUC_{0\text{-last}}$ (day·ng/mL)	$AUC_{0\text{-}\infty}$ (day·ng/mL)	$t_{1/2}$ (day)
Study 8201-470							
0.3	1	Positive	0.0119	1.0417	0.0142	-	-
1	6	Positive	0.0268 ± 0.0059	1.0417	0.111 ± 0.034	-	-
Study 8213480							
3	5	Positive	0.08 ± 0.007	2.0208	0.43 ± 0.05	0.49 ± 0.05	2.98 ± 0.72
3	1	Negative	0.07	1.0208	0.46	0.53	3.02

Mean ± SD; * Median

3.(ii).A.(2).2) Repeat-dose administration

i) Brentuximab vedotin

Brentuximab vedotin 0.3, 1, 3, or 10 mg/kg was intravenously administered in female rats once a week for 2 doses in total, and serum concentrations of brentuximab vedotin, TAb, and MMAE were determined [the table below]. PAHA was tested by ELISA, and the expression of RAHA was confirmed only in the 0.3 mg/kg group after administration of brentuximab vedotin (1 of 9 rats [11%]). The exposure to brentuximab vedotin, TAb, and MMAE (C_{max}, $AUC_{0\text{-}1d}$) increased generally in a dose-proportional manner within the dose range from 0.3 to 10 mg/kg. No accumulations of brentuximab vedotin and TAb were observed after the repeated doses.

The exposure (C_{max}, $AUC_{0\text{-}1d}$) to MMAE after dosing of brentuximab vedotin 10 mg/kg was lower than that after rapid intravenous injection of MMAE 0.2 mg/kg, which is equimolar with brentuximab vedotin 10 mg/kg (C_{max} of 29.7 and 50.2 ng/mL after the first and second doses, respectively; $AUC_{0\text{-}1d}$ of 16.2 and 25.6 day·ng/mL, respectively). MMAE showed a T_{max} of 1 day and was detectable up to Day 7 of administration of brentuximab vedotin 10 mg/kg, but showed

a T_{max} of 0.00347 day and became undetectable on and after Day 2 of rapid intravenous injection of MMAE 0.2 mg/kg. The applicant explained that the mean residence time could not be analyzed due to the limited number of blood sampling points in this study.

PK parameters of brentuximab vedotin and TAb following repeated intravenous administration of brentuximab vedotin for 2 weeks to female rats

	Dose (mg/kg)	n*1	Number of doses	C_{max} (μg/mL)	T_{max} (day)	$AUC_{0\text{-}1d}$ (day·μg/mL)
Brentuximab vedotin	0.3	8*2	1	6.80	0.00347	4.06
			2	4.96	0.00347	3.13
	1	9	1	21.0	0.00347	13.1
			2	17.2	0.00347	11.2
	3	9	1	50.8	0.00347	32.8
			2	53.6	0.00347	35.8
	10	9	1	283	0.00347	181
			2	238	0.00347	167
TAb	0.3	8*	1	6.04	0.00347	3.96
			2	5.85	0.00347	4.00
	1	9	1	20.2	0.00347	14.0
			2	20.2	0.00347	13.9
	3	9	1	59.7	0.00347	40.2
			2	54.0	0.00347	38.9
	10	9	1	261	0.00347	175
			2	192	0.00347	148

Arithmetic means; *1, Blood samples were collected from different rats at each time point; *2, One RAHA-positive animal was excluded.

PK parameters of MMAE following repeated intravenous administration of brentuximab vedotin for 2 weeks to female rats

Dose (mg/kg)	n*1	Number of doses	C_{max} (ng/mL)	T_{max} (day)	$AUC_{0\text{-}1d}$ (day·ng/mL)
0.3	8*2	1	0.0111	1.00	-
		2	0.0152	1.00	-
1	9	1	0.0410	1.00	0.0295
		2	0.0544	1.00	0.0374
3	9	1	0.138	1.00	0.0901
		2	0.154	1.00	0.105
10	9	1	0.463	1.00	0.317
		2	0.708	1.00	0.442

Arithmetic means; *1, Blood samples were collected from different rats at each time point; *2, One RAHA-positive animal was excluded.

Brentuximab vedotin 2 or 3 mg/kg was intravenously administered in male and female cynomolgus monkeys once a week for 4 doses in total (the fourth dose was administered only to 2 of 4 animals in the 2 mg/kg group and not administered to animals in the 3 mg/kg group), and serum concentrations of brentuximab vedotin, TAb, and MMAE were determined [the table below]. PAHA was tested by ELISA and 3 of 4 animals (75%) each in the 2 and 3 mg/kg groups were confirmed positive for PAHA after administration of brentuximab vedotin. Serum concentrations of brentuximab vedotin decreased below the lower limit of quantitation (6.25 ng/mL) on and after Days 26 and 21 of the first dose in PAHA-positive animals in the 2 and 3 mg/kg groups, respectively, and PAHA-positive animals showed a more rapid decline in serum concentrations of brentuximab vedotin compared with PAHA-negative animals. The PK parameters of MMAE after the fourth dose were similar to those after the first dose.

PK parameters of brentuximab vedotin and TAb following repeated intravenous administration of brentuximab vedotin for 4 weeks to male and female cynomolgus monkeys

	Dose of brentuximab vedotin (mg/kg)	n	PAHA	Number of doses	C_{max} (μg/mL)	T_{max} *1 (day)	AUC (day·μg/mL)	C_{max} Accumulation ratio (fourth dose/ first dose)	AUC accumulation ratio (fourth dose/ first dose)
Brentuximab vedotin	2	1	Negative	1	57.83	0.0625	104.80	0.9	0.9
				4	52.73	0.0278	97.83		
		3	Positive	1	51.84 ± 6.14	0.0278	98.17 ± 7.40	0.6	0.2
				4	33.59*2	0.0278*2	21.26*2		
	3*3	1	Negative	1	90.33	0.0278	193.24	-	-
				4	-	-	-		
		3	Positive	1	89.66 ± 8.76	0.0278	201.52 ± 11.11	-	-
				4	-	-	-		
TAb	2	1	Negative	1	105.40	0.5208	164.81	1.1	1.1
				4	110.90	0.5208	181.41		
		3	Positive	1	58.13 ± 7.47	0.0278	166.50 ± 15.51	0.7	0.2
				4	38.21*2	0.0278*2	30.29*2		
	3*3	1	Negative	1	74.76	0.0278	204.1	-	-
				4	-	-	-		
		3	Positive	1	90.55 ± 11.21	0.0278	221.43 ± 48.71	-	-
				4	-	-	-		

Arithmetic means ± SD; *1, Median; *2, n = 1; *3, The fourth dose was not administered.

PK parameters of MMAE following repeated intravenous administration of brentuximab vedotin for 4 weeks to male and female cynomolgus monkeys

	Dose of brentuximab vedotin (mg/kg)	n	PAHA	Number of doses	C_{max} (ng/mL)	T_{max} *1 (day)	AUC (day·ng/mL)	C_{max} Accumulation ratio (fourth dose/ first dose)	AUC accumulation ratio (fourth dose/ first dose)
MMAE	2	1	Negative	1	0.05	2.0208	0.23	1.4	1.4
				4	0.07	1.208	0.33		
		3	Positive	1	0.05 ± 0.006	2.0208	0.23 ± 0.03	2.2	1.3
				4	0.11*2	1.0208*2	0.30*2		
	3*3	1	Negative	1	0.07	3.0208	0.38	-	-
				4	-	-	-		
		3	Positive	1	0.07 ± 0.004	2.0208	0.34 ± 0.02	-	-
				4	-	-	-		

Arithmetic means ± SD; *1, Median; *2, n = 1; *3, The fourth dose was not administered.

Brentuximab vedotin 1 or 3 mg/kg was intravenously administered in male and female cynomolgus monkeys once every 3 weeks for 9 doses in total, and serum concentrations of brentuximab vedotin, TAb, and MMAE were determined [the table below]. PAHA was tested by ECL and 39 of 40 animals excluding 1 male in the 3 mg/kg group were confirmed positive for PAHA after administration of brentuximab vedotin.

Using a linear threshold model, regression was performed between the accumulation indexes of MMAE (the radio of C_{max} after the ninth dose to C_{max} after the first dose [C_{max} AI], the radio of AUC after the ninth dose to AUC after the first dose [AUC AI]) and the titer of PAHA. As a result, the upper limit of the 95% confidence interval (CI) of the antibody titer threshold based on correlation with AUC AI was 26,132 and 13,614 for female and male animals, respectively, and

that based on correlation with C_{max} AI was 3177 and 7699 for female and male animals, respectively; animals with the antibody titers exceeding the thresholds tended to show increased AUC AI and C_{max} AI of MMAE. Stratification of PK parameters of brentuximab vedotin, TAb, and MMAE based on the PAHA titer (geometric means on Days 148 and 176) are shown by dose level in the table below. In the high PAHA titer subgroup, exposure to MMAE was higher and exposures to brentuximab vedotin and TAb were lower on Day 169 than those on Day 1. In the low PAHA titer subgroup, however, no clear differences were observed in exposures to brentuximab vedotin, TAb, and MMAE between Day 1 and Day 169. In addition, in the high PAHA titer subgroup, T_{max} of MMAE substantially decreased after the ninth dose (to approximately 1.5 hours) compared with that after the first dose (approximately 2 days).

The applicant explained that the increase in exposure to MMAE in the high PAHA titer subgroup may be caused by an apparent increase in MMAE concentration in circulation resulting from binding of PAHA to the MMAE moiety in brentuximab vedotin, but that the definite reason for the observed increase in exposure to MMAE and reduction of T_{max} after repeated doses was unknown.

PK parameters of brentuximab vedotin and TAb following repeated intravenous administration of brentuximab vedotin for 26 weeks to male and female cynomolgus monkeys

	Dose (mg/kg)	PAHA titer[*1]	n	Number of doses	C_{max}[*2] (μg/mL)	AUC[*2, *3] (day·μg/mL)
Brentuximab vedotin	1	High	13	1	27.1 ± 5.6	48.0 ± 4.3
				9	0.231 ± 0.703	0.028 ± 0.080[*4]
		Low	7	1	25.8 ± 3.9	41.7 ± 7.7
				9	13.798 ± 17.689	18.8 ± 21.7[*5]
	3	High	7	1	83.5 ± 16.8	157.1 ± 23.3
				9	0.048 ± 0.077	0[*6]
		Low	13	1	83.3 ± 14.5	182.5 ± 37.8
				9	87.353 ± 38.877	186.349 ± 98.422[*7]
TAb	1	High	13	1	26.0 ± 5.1	61.8 ± 7.1
				9	0.006 ± 0.022	0[*8]
		Low	7	1	25.7 ± 4.6	56.2 ± 8.7
				9	10.4 ± 13.5	15.0 ± 20.6[*9]
	3	High	7	1	79.3 ± 15.9	201.6 ± 46.5
				9	0	0
		Low	13	1	78.8 ± 13.7	227.9 ± 43.1
				9	70.306 ± 33.840	225 ± 121[*4]

Arithmetic means ± SD; *1, Stratification was performed based on the upper limit of 95% CI of the antibody titer threshold based on correlation with C_{max} AI (3177 females, 7699 males) obtained from a linear threshold model; *2, At any time points, measurements in animals with serum concentrations of brentuximab vedotin and TAb below the lower limit of quantitation were considered as 0; *3, $AUC_{0\text{-}21d}$ was used for the first dose and $AUC_{168\text{-}189d}$ for the ninth dose; *4, n = 8; *5, n = 4; *6, n = 3; *7, n = 11; *8, n = 12; *9, n = 5

PK parameters of MMAE following repeated intravenous administration of brentuximab vedotin for 26 weeks to male and female cynomolgus monkeys

	Dose (mg/kg)	PAHA titer*1	n	Number of doses	C_{max}*2 (ng/mL)	AUC*2, 3 (day·μg/mL)
MMAE	1	High	13	1	0.0317 ± 0.0106	0.1528 ± 0.0614
				9	7.59 ± 11.98	7.43 ± 14.58
		Low	7	1	0.0278 ± 0.0113	0.1284 ± 0.0554
				9	0.092 ± 0.071	0.190 ± 0.040
	3	High	7	1	0.0824 ± 0.0233	0.4917 ± 0.1696
				9	16.37 ± 19.96	18.13 ± 24.59
		Low	13	1	0.0841 ± 0.0390	0.5142 ± 0.2473
				9	0.134 ± 0.090	0.367 ± 0.244

Arithmetic means ± SD; *1, Stratification was performed based on the upper limit of 95% CI of the antibody titer threshold based on correlation with C_{max} AI (3177 females, 7699 males) obtained from a linear threshold model; *2, At any time points, measurements in animals with serum levels of MMAE below the lower limit of quantitation were considered as 0; *3, $AUC_{0\text{-}21d}$ was used for the first dose and $AUC_{168\text{-}189d}$ for the ninth dose.

ii) MMAE

MMAE 0.0097, 0.097, or 0.194 mg/kg was intravenously administered in male and female rats once a week for 4 doses in total, and serum concentrations of MMAE were determined [the table below].

$AUC_{0\text{-}24h}$ of MMAE increased generally in a dose-proportional manner, but the increase in C_{max} was less than dose-proportional. In light of the rapid decrease in plasma concentrations of MMAE immediately after dosing, C_{max} of MMAE increased in a less than dose-proportional manner possibly because difference in timing of blood sampling had an impact on the measurements of C_{max}. After the first dose, no apparent gender-related differences in C_{max} and $AUC_{0\text{-}24h}$ of MMAE were observed in the 0.0097 or 0.097 mg/kg groups, while males showed lower C_{max} and $AUC_{0\text{-}24h}$ values than females in the 0.194 mg/kg group. After the fourth dose, however, no apparent gender-related differences in C_{max} and $AUC_{0\text{-}24h}$ of MMAE were observed in the 0.0097 mg/kg group, while males showed higher C_{max} and $AUC_{0\text{-}24h}$ values than females in the 0.097 and 0.194 mg/kg groups, unlike after the first dose. From these results, the presence or absence of gender-related differences in PK of MMAE in rats is not clear because, for example, there is a tendency for the results to vary depending on the number of dose and dose level, in spite of the gender-related differences in exposure to MMAE observed in some dose groups. In addition, the applicant explained that V_d of MMAE was higher than the plasma volume of rats (0.0396-0.0416 L/kg) (*J Appl Physiol*. 1994;76:485-9, *J Nucl Med*. 1985;26:72-6), suggesting an extensive tissue distribution of MMAE.

PK parameters of MMAE following repeated intravenous administration of MMAE for 4 weeks to male and female rats

Dose (mg/kg)	Gender	Day of measurement	C_{max} (ng/mL)	AUC_{0-24h} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	$t_{1/2}$ (h)	V_d (mL/kg)	CL (mL/h/kg)
0.0097	Males	1	0.593	2.610	2.747	5.76	29,327	3531
		22	0.698	3.984	4.123	5.17	17,559	2353
	Females	1	0.495	2.567	2.686	5.65	29,425	3612
		22	0.840	3.067	3.140	4.68	20,848	3089
0.097*	Males	1	3.530	25.698	32.293	10.9	47,223	3004
		22	5.490	52.445	-	-	-	-
	Females	1	3.750	28.591	-	-	-	-
		22	4.835	28.600	-	-	-	-
0.194*	Males	1	5.795	49.414	-	-	-	-
		22	11.050	70.993	-	-	-	-
	Females	1	12.550	91.009	-	-	-	-
		22	7.005	49.184	-	-	-	-

Two animals/time point (blood samples were collected from different rats at each time point); *, $t_{1/2}$, $AUC_{0-\infty}$, V_d, and CL were not evaluated because the serum concentrations of MMAE had no clear terminal phase except for males in the 0.097 mg/kg group after the first dose.

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

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

A single intravenous dose of ^{3}H-labeled MMAE 0.057 mg/kg (mean dose) was administered to male rats and tissue distribution of radioactivity was determined by quantitative whole-body autoradiography (QWBA). Most of the radioactivity in the plasma was eliminated from the systemic circulation within 4 hours post-dose, and radioactivity distributed rapidly and extensively to tissues. Tissues with high radioactivity (C_{max} ≥0.20 μg eq/g) included the anterior pituitary gland, lung, renal cortex, and renal medulla (0.520, 0.242, 0.232, and 0.217 μg eq/g, respectively). On the other hand, radioactivity in the brain, spinal cord, and lens was below the lower limit of quantitation (0.003 μg eq/g) at any measurement point. Radioactivity was eliminated in most tissues within 96 hours post-dose, but detected in the thymus, anterior pituitary gland, posterior pituitary gland, and uvea (0.013, 0.006, 0.005, and 0.009 μg eq/g, respectively). The applicant explained that MMAE was suggested to bind to melanin based on the fact that weak radioactivity (0.005 μg eq/g) was detected in the uvea even 28 days after administration. No tissue distribution studies of brentuximab vedotin and cAC10 have been conducted.

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

^{3}H-labeled MMAE (1, 10, 100 nmol/L) was incubated with mouse, rat, monkey, and human plasma samples, and the plasma protein binding rate was investigated by the ultracentrifugation method. The plasma protein binding rate (mean rates at each concentration) was 18.8% to 28.5% in mouse plasma, 72.0% to 73.5% in rat plasma, 17.1% to 18.9% in monkey plasma, and 67.9% to 82.2% in human plasma, showing that the values were higher in rats and humans than in mice and monkeys. In addition, in mice and humans, plasma protein binding rate tended to increase with increasing concentrations of MMAE.

Following intravenous administration of brentuximab vedotin 3 mg/kg containing ^{3}H-labeled MMAE in male and female rats, the blood-to-plasma ratio of radioactivity concentration (mean ratios at each time point) between 15 minutes and 336 hours post-dose ranged from 0.644 to 0.909. In addition, following intravenous administration of ^{3}H-labeled MMAE 0.056 mg/kg in male and female rats, the blood-to-plasma ratio of radioactivity concentration (mean ratios at each time point) between 15 minutes and 336 hours post-dose ranged from 1.332 to 7.062. Thus, the applicant explained that it was suggested that MMAE was distributed to blood cells.

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

Brentuximab vedotin 0.3, 1, 3, or 10 mg/kg was administered intravenously to pregnant rats on gestation days 6 and 13, and serum concentrations in dams and fetuses and amniotic fluid concentrations of brentuximab vedotin, TAb, and MMAE on gestation day 18 were determined [the table below].

No fetuses were found in all rats in the brentuximab vedotin 10 mg/kg group. The applicant explained that administration of brentuximab vedotin was considered to lead to fetal transfer of brentuximab vedotin, TAb, and MMAE across the placenta based on the fact that brentuximab vedotin, TAb, and MMAE were detected in fetal serum although all these levels in the fetuses were lower than those in the dams.

Serum and amniotic concentrations of brentuximab vedotin, TAb, and MMAE after repeated intravenous administration of brentuximab vedotin to pregnant rats

	Dose (mg/kg)	Dam serum (μg/mL)	Fetal serum (μg/mL)	Amniotic (μg/mL)
Brentuximab vedotin	0.3	0.137 ± 0.056[*1]	0.0309 ± 0.0176[*1]	0[*1]
	1	0.574 ± 0.094[*1]	0.1 ± 0.026[*1]	0.00301 ± 0.00598[*1]
	3	4.41 ± 0.92[*1]	-	0.0758, 0.0329
TAb	0.3	0.326 ± 0.138[*1]	0.0708 ± 0.0476[*1]	0
	1	1.26 ± 0.15[*1]	0.187 ± 0.052[*1]	0.0257 ± 0.0168[*1]
	3	9.81 ± 1.97[*2]	-	0.241, 0.118
MMAE	0.3	0[*1]	0.0376 ± 0.0112[*1]	0.0189 ± 0.0093[*1]
	1	0.0012 ± 0.00360[*1]	0.188 ± 0.029[*1]	0.205 ± 0.192[*1]
	3	0.028 ± 0.0044[*1]	-	2.16, 0.155

Arithmetic means ± SD; Values below the lower limit of quantitation were considered as 0 μg/mL; *1, n = 9; *2, n = 7

3.(ii).A.(4) Metabolism

In the application for brentuximab vedotin, non-clinical data on metabolism studies using MMAE were submitted, but data on studies using brentuximab vedotin were not submitted. The applicant explained that cAC10 was considered to be degraded into single amino acids in the body after the release of MMAE from brentuximab vedotin, and thus only studies using MMAE were conducted as non-clinical studies regarding metabolism; studies using brentuximab vedotin were not conducted.

3.(ii).A.(4).1) *In vitro* metabolism

^{3}H-labeled MMAE (10 μmol/L) was incubated with rat, cynomolgus monkey, and human hepatocytes at 37°C for 4 hours, and formation of metabolites of brentuximab vedotin was investigated. The percent elimination of MMAE in rat, cynomolgus monkey, and human hepatocytes was 32%, 18%, and 32%, respectively, indicating no apparent species differences. A total of 12 metabolites were detected in cynomolgus monkey hepatocytes. Of these 12 metabolites, 9 were detected in rat hepatocytes and a different combination of 9 were also detected in human hepatocytes. No human-specific metabolites were detected.

^{3}H-labeled MMAE (0.9, 10, 100 μmol/L) was incubated with human liver microsomes in the presence of nicotinamide-adenine dinucleotide phosphate (NADPH) at 37°C for 40 minutes. As a result, C4 (*O*-demethyl form), C7 (*N*-demethyl form), and C8 (ketone form) were detected as the main metabolites. In addition, ^{3}H-labeled MMAE (6 and 16 μmol/L) was incubated with recombinant human CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), and CYP isozymes involved in metabolism of brentuximab vedotin were investigated. C4, C7, and C8 were detected in the CYP3A4 expression system, and C7 was detected in the CYP2D6 expression system. Furthermore, the study in human liver microsomes showed a correlation between CYP3A4 activity and formation of C4, C7, and C8, as well as a substantial inhibition of formation of C4, C7, and C8 by CYP3A4 inhibitor or anti-CYP3A4 monoclonal antibody.

Based on the above, the applicant explained that these results suggested that CYP3A4 mainly contributed to the metabolism of MMAE.

3.(ii).A.(4).2) *In vivo* metabolism

A single dose of 3 mg/kg of brentuximab vedotin containing ^{3}H-labeled MMAE was administered intravenously to male and female rats, and metabolites in feces and urine were investigated. As a result, brentuximab vedotin was not detected in feces or urine, and the main fecal and urinary metabolites were both found to be MMAE. In addition, C4 was detected as another fecal metabolite. The applicant explained that other 5 metabolites were detected in urine but not identified since they existed in trace amounts.

3.(ii).A.(5) Excretion

3.(ii).A.(5).1) Urinary and fecal excretion

Following a single intravenous dose of brentuximab vedotin 3 mg/kg containing ^{3}H-labeled MMAE in male and female rats, approximately 50% of the administered radioactivity was excreted in feces and urine within 48 hours post-dose, and the fecal excretion rate of radioactivity (% of dose) up to 672 hours post-dose was 89.3% and 96.9% in males and females, respectively, and the urinary excretion rate was 14.3% and 7.1%, respectively.

Following a single intravenous dose of ^{3}H-labeled MMAE 0.056 mg/kg in male and female rats, approximately 95% of the administered radioactivity was excreted in feces and urine within 48 hours post-dose, and the fecal excretion rate of radioactivity up to 672 hours post-dose was 96.7% and 102% in males and females, respectively, and the urinary excretion rate was 15.1% and 9.4% in males and females, respectively. No gender-related differences in urinary and fecal excretion were observed in either of the studies.

The applicant explained that, as shown above, radioactivity was mainly excreted in feces both after administration of brentuximab vedotin containing ^{3}H-labeled MMAE and after administration of ^{3}H-labeled MMAE, and that the radioactivity was excreted more rapidly from the group of animals treated with ^{3}H-labeled MMAE than from the group of animals treated with brentuximab vedotin containing ^{3}H-labeled MMAE.

3.(ii).A.(5).2) Excretion in milk

Excretion of brentuximab vedotin and MMAE in milk was not investigated and remains unknown. Therefore, the applicant explained that the package insert was going to caution that lactating women should stop lactation or avoid use of brentuximab vedotin.

3.(ii).A.(6) Pharmacokinetic interactions

3.(ii).A.(6).1) Enzyme inhibition

Substrates of CYP species (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) were incubated with human liver microsomes in the presence of MMAE (0.1-100 μmol/L). As a result, MMAE inhibited metabolism of midazolam, a substrate of CYP3A4/5 (IC_{50}, 10 μmol/L), but did not inhibit metabolism of testosterone, also a substrate of CYP3A4/5. MMAE did not show an apparent inhibitory effect on metabolism of substrates of the other CYP species.

The substrates of above CYP species were preincubated with human liver microsomes in the presence of MMAE (0.1-100 μmol/L) and NADPH for 30 minutes. As a result, MMAE inhibited CYP3A4/5-mediated metabolism of testosterone and midazolam in a time-dependent manner. In addition, the time-dependent inhibition of CYP3A4/5 by MMAE was investigated based on 6β-hydroxylation of testosterone. A rate constant of irreversible inactivation (K_{inact}) was 0.10 min^{-1} and an inhibition constant (K_i) was 1.12 μmol/L, leading to a K_{inact}-to-K_i ratio of 90 mmol/L/min.

3.(ii).A.(6).2 Enzyme induction

Human hepatocytes were treated with MMAE (0.1, 1, 10 μmol/L) for 3 days. As a result, enzyme activities (percentage relative to the vehicle control) of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4/5 decreased to 49% to 55%, 62% to 70%, 55% to 63%, 34% to 47%, 35% to 39%, and 32% to 53%, respectively. Thus, it is considered that no findings indicating induction of CYP species by MMAE were found. The applicant explained that the results from this study were inconsistent with the preceding results indicating no inhibition of CYP species excluding CYP3A4 by MMAE [see "3.(ii).A.(6).1 Enzyme inhibition"], but that the clinical significance of these study results is unknown because MMAE did not inhibit any CYP species in a concentration-dependent manner and because MMAE treatment did not induce marked changes in hepatocyte morphology or inhibit cell proliferation.

3.(ii).A.(6).3 Transporters

The membrane permeability of MMAE (1, 10, 100 μmol/L) was investigated using human colon carcinoma-derived Caco-2 cell line. As a result, the ratio of the apparent permeability from apical surface to basolateral surface ($P_{app\ A\rightarrow B}$) to that from basolateral surface to apical surface ($P_{app\ B\rightarrow A}$) ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$, efflux ratio) was 15, 34, and 49 for 1, 10, and 100 μmol/L of MMAE, respectively, suggesting that MMAE is a substrate of efflux transporters expressed in Caco-2 cell line. The P-gp-mediated membrane permeability of 10 μmol/L MMAE was investigated using Caco-2 cell line. As a result, the efflux ratio of MMAE was 28, and the ratio decreased to 2.9 and 1.3 in the presence of P-gp inhibitor verapamil (60 μmol/L) and PSC833 (10 μmol/L), respectively. In addition, in another study using Caco-2 cell line, the efflux ratio of MMAE (10 μmol/L) was 8.8, and the ratio changed to 1.6 in the presence of a P-gp inhibitor LY335979 (10 μmol/L), to 6.0 in the presence of a breast cancer resistance protein (BCRP) inhibitor Ko143 (5 μmol/L), and to 4.3 in the presence of a multidrug resistance-associated protein (MRP)-2 inhibitor indometacin (100 μmol/L). Using Chinese hamster ovary (CHO) cell line engineered to express human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 2, and organic anion transporter (OAT) 1 as well as HEK-293 cell line engineered to express human OAT3, OATP1B1-, OATP1B3-, OCT2-, OAT1-, and OAT3-mediated transport of ^{3}H-labeled MMAE (10, 100 nmol/L) were investigated. As a result, internalization of radioactivity in these cell lines was similar to that observed in the control group (CHO or HEK-293 cell line), and no clear effects on internalization of radioactivity were observed even in the presence of an inhibitor of each individual transporter. The applicant explained that, based on the above, MMAE was considered to be a substrate of P-gp but not a substrate of BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

In addition, inhibition of P-gp-mediated transport of digoxin (10 μmol/L) by MMAE was investigated using Caco-2 cell line. As a result, the efflux ratio of digoxin was 14 and 11 in the absence and presence of MMAE (50 μmol/L), respectively, and the inhibition of P-gp-mediated transport of digoxin by MMAE was limited, with the IC_{50} value of ≥50 μmol/L. The applicant explained that, based on the above, no findings of clinical concern were found in terms of inhibition of P-gp by MMAE.

3.(ii).A.(7) Other properties

3.(ii).A.(7).1 Stability of brentuximab vedotin in plasma

Brentuximab vedotin (0.33 mg/mL) was incubated with the control (phosphate-buffered saline containing 1% bovine serum albumin) or rat, monkey, or human plasma at 37°C for 3 weeks, and stability of brentuximab vedotin in plasma was investigated. As a result, the proportion (% of added amount) of MMAE released into the plasma was 0.147% in the control, 2.048% in rat plasma, 0.374% in monkey plasma, and 0.527% in human plasma, indicating that the stability of brentuximab vedotin in monkey and human plasma did not differ substantially from that observed in the control group. The applicant explained that the definite reason why the slight instability of

brentuximab vedotin had been observed in rat plasma as compared with monkey and human plasma was unknown.

3.(ii).A.(7).2) Intracellular catabolism of brentuximab vedotin

Unlabeled or ^{14}C-labeled brentuximab vedotin (200 ng/mL) was incubated with CD30-positive cells (Karpas 299, L428, and L540cy cell lines) or CD30-negative cells (WSU-NHL and Ramos cell lines) at 37°C for 3 days, and the catabolism of brentuximab vedotin was investigated. As a result, in CD30-negative cells, MMAE was not detected in the cellular fraction or cell culture at any time points. In CD30-positive cells, however, MMAE was detected both in the cellular fraction and in cell culture, and the intracellular MMAE concentrations reached ≥400 nmol/L within 24 hours after addition of brentuximab vedotin. The applicant explained that the above intracellular MMAE concentrations were consistent among the methods used (radiometry, mass spectrometry, bioassay), indicating that MMAE is generated by the catabolism of brentuximab vedotin.

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

Based on the submitted data and the following reviews, PMDA concluded that the applicant's discussions on absorption, distribution, metabolism, and excretion and pharmacokinetic interactions of brentuximab vedotin are acceptable.

Tissue distribution of brentuximab vedotin

PMDA asked the applicant to explain the reason for not having conducted studies on tissue distribution of brentuximab vedotin and cAC10.

The applicant responded as follows:
Studies on tissue distribution of brentuximab vedotin and cAC10 have not been conducted because it might be discussed with the following considerations:

- Brentuximab vedotin is an ADC consisting of IgG1 monoclonal antibody (cAC10) and MMAE, which is covalently bound to the antibody by a linker, and the antigen-nonspecific distribution of brentuximab vedotin and cAC10 is considered to be similar to that of endogenous IgGs. The tissue cross-reactivity study revealed that antigen-specific distribution is dependent on the expression of CD30 [see "3.(i).A.(1).2).i) Binding characteristics to CD30-positive cells and recombinant CD30 proteins" and "3.(iii).A.(6).4) Cross-reactivity studies"].

- Tissue distribution of brentuximab vedotin is considered to be limited based on the evaluation results of distribution volume of brentuximab vedotin in the single-dose studies in rats and cynomolgus monkeys [see "3.(ii).A.(2).1) Single dose administration"].

Since MMAE was suggested to bind to melanin [see "3.(ii).A.(3).1) Tissue distribution"], PMDA asked the applicant to explain the safety concerns due to distribution of MMAE or its metabolites to melanin-containing tissues during clinical use of brentuximab vedotin.

The applicant responded as follows:
The results of the single-dose study of MMAE in pigmented rats did not show binding of MMAE-related substances to skin tissues, but showed reversible binding to the uvea (a melanin-containing tissue) and slow elimination from the uvea. Therefore, the possibility cannot be ruled out that repeated doses of brentuximab vedotin in a clinical setting would lead to accumulation of MMAE in melanin-containing tissues due to binding of MMAE to these tissues. However, taking into account that MMAE concentrations in melanin-containing tissues are expected to be low due to the slow release of MMAE from brentuximab vedotin, ADC, and that no toxicity attributed to the binding of MMAE, which is photostable, to melanin has been observed in monkeys [see

"3.(iii).A.(2) Repeat-dose toxicity"], toxicity resulting from the binding of MMAE to melanin is unlikely to occur also in clinical settings. In addition, no clear differences were observed in toxicities in melanin-containing tissues such as the skin and eye between the Japanese and Caucasian population based on the results from foreign phase II studies (Studies SG035-0003 and SG035-0004) and a Japanese phase I/II study (Study TB-BC010088).

Based on the above, safety concerns with brentuximab vedotin due to distribution of MMAE or its metabolites to melanin-containing tissues are considered to be limited.

PMDA considers as follows:
Brentuximab vedotin and cAC10 are considered to poorly distribute into tissues and mainly distribute to blood vessels, and the safety profiles of brentuximab vedotin have been evaluated to a certain degree in humans. Therefore, studies on tissue distribution of brentuximab vedotin and cAC10 are not mandated.

It is necessary to be careful about the occurrence of adverse events suggesting an association with distribution of MMAE or its metabolites to melanin-containing tissues in clinical use because non-clinical studies suggested the possibility that MMAE or its metabolites may be distributed to the uvea (a melanin-containing tissue) for an extended period.

3.(iii) Summary of toxicology studies

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

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

No deaths due to brentuximab vedotin were observed either in a study of single intravenous administration of brentuximab vedotin at doses of 0 (vehicle control), 3, and 15 mg/kg in male and female SD rats or in a study of single intravenous administration of brentuximab vedotin at doses of 1, 2, 3, 4, and 6 mg/kg in male and female cynomolgus monkeys. Therefore, the approximate lethal doses in rats and monkeys were determined to be >15 mg/kg and >6 mg/kg, respectively.

In a study of single intravenous administration of brentuximab vedotin at doses of 0 (vehicle control), 0.5, 5, and 10 mg/kg or MMAE at doses of 0 (vehicle control), 0.01, 0.1, and 0.2 mg/kg in male and female SD rats, no deaths were observed in the brentuximab vedotin group, but all animals in the MMAE 0.2 mg/kg group became moribund and were euthanized 2 days after administration. A thickening or hyperplasia of bile duct epithelium and a single cell necrosis of hepatocytes were observed in the brentuximab vedotin ≥5 mg/kg groups and the MMAE ≥0.1 mg/kg groups, and bone marrow toxicity (e.g., decrease in myeloid cell count, decrease in total leukocyte count) and depletion of thymic lymphoid tissue were observed in the brentuximab vedotin 10 mg/kg groups and the MMAE ≥0.1 mg/kg groups. Thus, the no observed adverse effect levels (NOAELs) of brentuximab vedotin and MMAE in rats were determined to be 0.5 mg/kg and 0.01 mg/kg, respectively.

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

3.(iii).A.(2).1) Four-week repeated intravenous dose toxicity study in rats

Brentuximab vedotin at doses of 0 (vehicle control), 0.5, 5, and 10 mg/kg, MMAE at doses of 0 (vehicle control), 0.0097, 0.097, and 0.194 mg/kg, and cAC10 at a dose of 10 mg/kg were intravenously administered to male and female SD rats once a week for 4 doses in total, with a 4-week recovery period incorporated after the last dose for some animals in each group. As a result, no deaths due to brentuximab vedotin, MMAE, or cAC10 were observed. A decreased production of red cell (decreases in reticulocyte count, red blood cell count, hemoglobin, and hematocrit) was observed in the brentuximab vedotin ≥5 mg/kg groups and the MMAE ≥0.097 mg/kg groups, and decreases in myeloid cell, thymus weight, and spermatocyte as well as a vacuolation of testicular Sertoli cells were observed in the brentuximab vedotin ≥5 mg/kg groups and the MMAE

0.194 mg/kg group (Sertoli cell vacuolation in the MMAE group was observed only in the group with recovery period at 4 weeks after the last dose). Increases in total bilirubin and γ-glutamyl transpeptidase, depletion of thymic lymphoid tissue, focal coagulative necrosis of the liver, azoospermia, and seminiferous tubular degeneration were observed in the brentuximab vedotin 10 mg/kg group and the MMAE 0.194 mg/kg group (The testicular findings in the MMAE group were observed only in the group with recovery period at 4 weeks after the last dose). These toxicity findings were reversible or tended to be reversible except for the testicular findings. The applicant explained that the absence of toxicity findings in the cAC10 group was consistent with the fact that cAC10 does not bind to rat CD30.

Based on the above results, the 4-week repeated-dose NOAELs of brentuximab vedotin and MMAE in rats were determined to be 0.5 mg/kg and 0.097 mg/kg, respectively. In addition, the highest non-severely toxic dose (HNSTD) of brentuximab vedotin was determined to be 5 mg/kg. The exposure ($AUC_{0\text{-}24h}$) to MMAE at the NOAEL was 25.7 ng·day/mL in males and 28.6 ng·day/mL in females, and was similar to the exposure to MMAE* observed after the first dose in Japanese HL or ALCL patients who received multiple doses of brentuximab vedotin.

* The exposure ($AUC_{0\text{-}\infty}$) to MMAE after the first dose of brentuximab vedotin (1.8 mg/kg) was 23.3 ng·day/mL in Study TB-BC010088.

3.(iii).A.(2).2) Eleven-week repeated intravenous dose toxicity study in cynomolgus monkeys

Brentuximab vedotin at doses of 0 (vehicle control), 1, 3, and 6 mg/kg and MMAE at a dose of 0.058 mg/kg (equimolar with 3 mg/kg of brentuximab vedotin) was intravenously administered to male and female cynomolgus monkeys every 3 weeks for 4 doses in total, with a 5-week recovery period incorporated after the last dose for some animals. As a result, 3 of 16 animals in the brentuximab vedotin 6 mg/kg group died or were euthanized due to bacterial infection secondary to severe neutrocytopenia; in these animals, cytopenia, necrosis, and bleeding in the bone marrow, multifocal coagulative necrosis of the liver, and lymphopenia in the thymus and spleen were observed. A decrease in all hematopoietic cells, bleeding, and increases in granuocytes and megakaryocytes in the bone marrow, and decreases in lymphoid cells in the thymus and spleen were observed in the brentuximab vedotin ≥1 mg/kg groups and the MMAE group. Since the findings in the brentuximab vedotin 1 mg/kg group were mild in severity, the NOAEL of brentuximab vedotin was determined based on the toxicity findings observed in the brentuximab vedotin ≥3 mg/kg. Decreases in albumin and inorganic phosphate levels, as well as necrosis and neutrocytopenia in the bone marrow were observed in the brentuximab vedotin ≥3 mg/kg groups and the MMAE group, and a decrease in thymus weight associated with depletion of lymphoid tissue in the thymus was observed in the brentuximab vedotin 6 mg/kg group.

Based on the above results, the 11-week repeated-dose NOAEL of brentuximab vedotin in monkeys was determined to be 1 mg/kg.

3.(iii).A.(2).3) Twenty-six-week repeated intravenous dose toxicity study in cynomolgus monkeys

Brentuximab vedotin at doses of 0 (vehicle control), 1, and 3 mg/kg was intravenously administered to male and female cynomolgus monkeys every 3 weeks for 9 doses in total, with a 6-week recovery period incorporated after the last dose for some animals. As a result, no deaths due to brentuximab vedotin were observed. Hunchback position, decreased activity, and pale face and pale oral mucosa were transiently observed after the sixth dose in 1 of 20 animals in the brentuximab vedotin 3 mg/kg group, but the relationship between these toxicity findings and treatment with brentuximab vedotin was unknown because these findings were not observed after the subsequent doses. A decrease in total leukocyte count mainly due to neutrocytopenia was observed in the brentuximab vedotin ≥1 mg/kg groups, and a decrease in large unstained cell count in females in the brentuximab vedotin 3 mg/kg group. No toxicity findings supporting the

NOAEL were observed in the brentuximab vedotin groups, since brentuximab vedotin-related effects were not found by histopathology procedures etc. in any groups. In addition, all the changes in hematological values observed in the brentuximab vedotin groups were reversible.

Based on the above results, the 26-week repeated-dose NOAEL in monkeys was determined to be 3 mg/kg. The exposure ($AUC_{0\text{-}21d}$) after the first dose at this dose was 189 μg·day/mL in males and 162 μg·day/mL in females, and was approximately 2.4- to 2.8-fold that observed after the first dose in Japanese HL or ALCL patients who received multiple doses of brentuximab vedotin.*

* The exposure ($AUC_{0\text{-}21d}$) after the first dose of brentuximab vedotin (1.8 mg/kg) was 66.76 μg·day/mL in Study TB-BC010088

3.(iii).A.(2).4) Six-week repeated intravenous dose toxicity study for cAC10 in cynomolgus monkeys

cAC10 at doses of 0 (vehicle control), 10, 50, or 100 mg/kg was intravenously administered to male and female cynomolgus monkeys once a week for 6 doses in total, with a 4-week recovery period incorporated after the last dose for some animals. As a result, no deaths due to cAC10 or findings related to cAC10 were observed.

Based on the above results, the 6-week repeated-dose NOAEL of cAC10 in monkeys was determined to be 100 mg/kg.

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

Genotoxicity studies of MMAE were conducted. No genotoxicity was observed in a bacterial reverse mutation assay or in a mutation assay in mouse lymphoma cells (L5178Y TK+/-). Since micronucleus induction was detected in a rat micronucleus assay, an additional study was performed. The results from the study showed that MMAE primarily induced centromere positive micronuclei formation; these results were considered consistent with the tubulin polymerization inhibitory activity of MMAE.

Genotoxicity studies of components of the linker moiety (maleimide, caproyl spacer, valine, citrulline, *p*-aminobenzyloxy carbonyl group) were conducted, and maleimide tested positive in the bacterial reverse mutation assay. Caproic acid tested negative in the bacterial reverse mutation assay, while valine, citrulline, and *p*-aminobenzyloxy carbonyl group were determined as non-mutagenic in an *in silico* analysis using the Deductive Estimation of Risk from Existing Knowledge (DEREK) for Windows Version 12 (Lhasa Limited).

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

Brentuximab vedotin is an antineoplastic drug intended for treatment of progressive cancer, and therefore no carcinogenicity study was conducted.

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

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

Brentuximab vedotin is an antineoplastic drug intended for treatment of progressive cancer, and therefore no study of fertility and early embryonic development to implantation was conducted.

Based on the facts that testicular toxicity was observed in the repeated-dose toxicity studies in rats [see "3.(iii).A.(2).1) Four-week repeated intravenous dose toxicity study in rats"] and that MMAE has an aneugenic potential [see "3.(iii).A.(3) Genotoxicity"], brentuximab vedotin may pose a potential risk to the fertility of male patients. Regarding effects of brentuximab vedotin on female reproductive organs, the applicant explained that although no effects on female reproductive organs such as the ovary were observed in the repeated-dose toxicity studies [see "3.(iii).A.(2) Repeat-dose toxicity"], slight staining specific to brentuximab vedotin in the fallopian tube was observed on the human tissue panel in the tissue cross-reactivity study [see

"3.(iii).A.(6).4) Cross-reactivity studies"], and therefore, the possibility cannot be ruled out that the toxicity due to the tubulin polymerization inhibitory activity of MMAE may affect the developing ovarian follicles or proliferative endometrium that are undergoing active cell division.

3.(iii).A.(5).2) Study for embryo-fetal development in rats

Brentuximab vedotin at doses of 0 (vehicle control), 0.3, 1, 3, and 10 mg/kg or MMAE at a dose of 0.2 mg/kg (equimolar with 10 mg/kg of brentuximab vedotin) was intravenously administered to pregnant SD rats on gestation day 6 and gestation day 13 for 2 doses in total, and caesarian section was performed on gestation day 21. Decreases in body weight, food consumption, and leukocyte and platelet counts, increases in reticulocyte count, hematocrit, and mean corpuscular volume, bone marrow hyperplasia, depletion of thymic lymphocytes, and extramedullary hematopoiesis in the spleen were observed in maternal animals in the brentuximab vedotin ≥3 mg/kg groups. A decrease in erythrocyte count and increases in neutrophil and monocyte counts were observed in maternal animals in the MMAE group. Regarding embryos and fetuses, increases in total resorptions of embryos, post-implantation deaths, and fetal deaths were observed in the brentuximab vedotin ≥3 mg/kg groups. Two live fetuses were found in the 3 mg/kg group, and umbilical hernia and malrotation of the hind limb were found in 1 each of the 2 live fetuses. No live fetuses were found in the 10 mg/kg group. Findings including increases in resorptions and post-implantation deaths were observed in the MMAE group, but the severity was less than that seen in the brentuximab vedotin 3 mg/kg and 10 mg/kg groups.

Based on the above results, the NOAEL of brentuximab vedotin for embryo-fetal development in rats was determined to be 1 mg/kg. The exposure ($AUC_{0\text{-last}}$) to MMAE at this dose was 0.0295 ng·day/mL and the exposure ($AUC_{0\text{-last}}$) to MMAE in the MMAE 0.2 mg/kg group was 16.2 ng·day/mL; these were lower than the exposure to MMAE[*1] observed after the first dose in Japanese HL or ALCL patients who received multiple doses of brentuximab vedotin. In addition, the exposure ($AUC_{0\text{-last}}$) to brentuximab vedotin in rats in the 3 mg/kg group was 83.3 μg·day/mL, and was similar to the exposure observed after the first dose in Japanese HL or ALCL patients who received multiple doses of brentuximab vedotin.[*2]

*1, The exposure ($AUC_{0\text{-}\infty}$) to MMAE after the first dose of brentuximab vedotin (1.8 mg/kg) was 23.3 ng·day/mL in Study TB-BC010088.

*2, The exposure ($AUC_{0\text{-}21d}$) to brentuximab vedotin after the first dose of brentuximab vedotin (1.8 mg/kg) was 66.76 μg·day/mL in Study TB-BC010088.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Immunotoxicity studies

In the 11-week repeated-dose toxicity study in cynomolgus monkeys [see "3.(iii).A.(2).2) Eleven-week repeated intravenous dose toxicity study in cynomolgus monkeys"], immunophenotyping in the brentuximab vedotin ≥3 mg/kg groups revealed a decrease in lymphocytes, a decrease in relative proportion of B lymphocytes (CD3-/CD20+), and an increase in relative proportion of CD3+ and CD3+/CD4+ T lymphocytes. However, changes in relative proportion of CD3+/CD8+ T lymphocytes or natural killer cells (CD3-/CD16+) were not found. Histopathology procedures revealed depletion of/decrease in lymphocytes in the thymic cortex and a decrease in lymphocytes in the germinal center of the spleen. The findings in the thymic cortex were resolved although a decrease in circulating B lymphocytes (CD3-/CD20+) was observed even during the recovery period. In the 26-week repeated-dose toxicity study [see "3.(iii).A.(2).3) Twenty-six-week repeated intravenous dose toxicity study in cynomolgus monkeys"], although a decrease in total leukocyte count (decrease in lymphocyte count) was observed without any histopathological changes in the brentuximab vedotin ≥1 mg/kg groups, the leukocyte and lymphocyte counts were resolved during the 6-week recovery period.

3.(iii).A.(6).2) Mechanistic studies of toxicity

Mechanistic studies of toxicity were conducted to fully investigate the time course of the bone marrow and testicular toxicities observed in the 4-week repeated-dose toxicity study in rats. As described below, the results from 2 single-dose toxicity studies to investigate the bone marrow toxicity and 1 repeated-dose toxicity study to investigate the testicular toxicity in rats demonstrated reversibility of these brentuximab vedotin-related toxicities.

- Following single intravenous administration of brentuximab vedotin at doses of 0 (vehicle control) and 10 mg/kg to female SD rats, 3 rats were euthanized every day up to 14 days post-dose, and the time course of the bone marrow toxicity was investigated. Bone marrow toxicities characterized by decrease in bone marrow cells, necrosis, and bleeding were observed, with the most significant impact being on neutrophils among myeloid cells, and pancytopenia was also observed. The decrease in bone marrow cells and associated changes were observed 1 to 5 days after administration, followed by regenerative responses (compensatory hyperplasia, left-shift/polychromasia of nuclei) from 5 to 12 days after administration and recovery 13 days after administration.

- Following single intravenous administration of MMAE at a dose of 0.2 mg/kg to female SD rats, 3 rats were euthanized every day up to 10 days post-dose and an additional 3 rats were euthanized 14 days after administration, and the time course of the bone marrow toxicity was investigated. MMAE was not well tolerated and 3 of 33 rats died within 4 days post-dose. The decrease in bone marrow cells and associated changes in hematological parameters were observed 2 to 5 days after administration, but subsequently regenerative responses were observed, and recovery was found within 7 to 8 days post-dose. In addition, 2 of 3 rats showed a multifocal lymphohistiocytic infiltration in the liver 10 days after administration.

- Following intravenous administration of brentuximab vedotin at doses of 0 (vehicle control) and 10 mg/kg to male SD rats once a week for 4 doses in total, and the reversibility, duration, and onset delay of toxicity findings during the recovery period from 4 days to 16 weeks after the last dose were investigated. Testicular toxicity (seminiferous tubular degeneration), hepatotoxicity (necrotizing hepatitis lesions, thickening/hyperplasia of the bile duct associated with epithelial necrosis and pericholangitis), and hematological findings (decreases in leukocyte and erythrocyte counts) were observed from 4 days after the last dose. The severity of the testicular toxicity increased 4 and 8 weeks after the last dose, but partial recovery was observed at 16 weeks after the lase dose. The effects on the liver and leukocyte and erythrocyte counts were shown to be reversible during the 16-week recovery period.

3.(iii).A.(6).3) Studies on metabolites

The growth inhibitory effect of the 3 metabolites of brentuximab vedotin (C4, C7, C8) [see "3.(ii).A.(4) Metabolism"] on Karpas 299, L540cy, and L428 cell lines were found to be similar to or lower than that of MMAE. In addition, the growth inhibitory effect of the metabolite C8 on primary human CD30-positive bone marrow cells was similar to that of MMAE, but those of C4 and C7 were lower than those of MMAE.

3.(iii).A.(6).4) Cross-reactivity studies

A tissue cross-reactivity study of biotinylated cAC10 using cynomolgus monkey and human normal tissues and a tissue cross-reactivity study of brentuximab vedotin using rat hepatic tissues and human tissues were conducted. Staining was observed in thyroid epithelial cells of cynomolgus monkeys, but the staining profile was not consistent with that of CD30 (*Am J Pathol*. 1994;145:276-80) and no impact on the thyroid gland was observed in the repeated-dose toxicity studies in monkeys, thus, its toxicological significance is unknown. In addition, brentuximab vedotin-specific binding was not found in rat hepatic tissues, while in human tissues, the

possibility of cross-reactivity to non-target tissues of brentuximab vedotin was suggested; the applicant explained that the toxicological significance of this cross-reactivity is unknown.

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

Based on the submitted data and the following reviews, PMDA concluded that the clinical use of brentuximab vedotin may be acceptable. However, caution should be exercised for the brentuximab vedotin-related testicular toxicity. In addition, embryo-fetal deaths were observed in the reproductive and developmental toxicity studies, brentuximab vedotin should be used in pregnant women or in women who may be pregnant only if the therapeutic benefits are expected to outweigh the potential risks to the fetus, and the risks to the fetus should be fully explained when it is necessary to use it in pregnant women.

3.(iii).B.(1) Genotoxicity of maleimide

Since maleimide was suggested to be genotoxic [see "3.(iii).A.(3) Genotoxicity"], PMDA asked the applicant to explain about the possibility of genotoxicity caused by maleimide released from brentuximab vedotin *in vivo*.

The applicant responded as follows:
Generation of free maleimide *in vivo* is unlikely, taking into account that brentuximab vedotin is stable in human plasma, as evidenced by the stability results of brentuximab vedotin based on the time course of MMAE release in human, rat, and cynomolgus monkey plasma [see "3.(ii).A.(7).1) Stability of brentuximab vedotin in plasma"]. In an *in vitro* study of distribution of an intermediate representing the linker-bound MMAE (SGD-1006) in plasma proteins using samples collected in Study SG035-0001, an amount of SGD-1006 equivalent to approximately 1.5% of brentuximab vedotin and free MMAE in plasma was shown to be distributed to plasma proteins such as albumin, but no definitive study results have been obtained regarding *in vivo* distribution of free maleimide after administration of brentuximab vedotin.

PMDA considers as follows:
The *in vivo* distribution of free maleimide after administration of brentuximab vedotin is unknown, thus, information on the genotoxicity results of maleimide should be appropriately provided via the package insert, etc.

3.(iii).B.(2) Differences in toxicity profile between brentuximab vedotin and MMAE

PMDA asked the applicant to explain the reason why testicular toxicity observed in the repeated-dose toxicity study in rats and embryo-fetal toxicity observed in the embryo-fetal study in rats were potentiated in animals receiving brentuximab vedotin compared with animals receiving the equimolar amount of MMAE.

The applicant responded as follows:
Taking into account that exposure to MMAE after administration of brentuximab vedotin was lower than that after administration of the equimolar amount of MMAE and that the residence time of MMAE after administration of brentuximab vedotin is considered to be longer than that after administration of the equimolar amount of MMAE [see "3.(ii).A.(2).2) Repeat-dose administration"], the testicular and embryo-fetal toxicities in rats seem to be attributed more to long term exposure to low-concentration MMAE following administration of brentuximab vedotin than to short term exposure to high-concentration MMAE.

PMDA considers as follows:
The above discussion by the applicant based on the toxicokinetics of MMAE is acceptable. The information on the findings of the testicular and embryo-fetal toxicities obtained from the toxicity studies in rats should be appropriately provided via the package insert, etc.

4. Clinical data

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

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

4.(i).A.(1) Analytical methods

4.(i).A.(1).1) Assay method for brentuximab vedotin (genetical recombination)

[redacted].

4.(i).A.(1).2) Assay method for total antibody (TAb)

[redacted].

4.(i).A.(1).3) Assay method for MMAE

Concentrations of MMAE in human plasma, urine, and feces were assayed by LC-MS/MS.

4.(i).A.(1).4) Assay method for anti-therapeutic antibody (ATA)

[redacted].

Samples in which anti-brentuximab vedotin antibodies (therapeutic antibody [ATA]) were detected by the above assay were subjected to an absorption test using brentuximab vedotin to determine whether they were ATA-positive or negative. In addition, samples which tested positive for ATA in the absorption test were subjected to a bioassay to determine the presence or absence of neutralizing antibodies. [redacted].

4.(i).A.(2) Impact of brentuximab vedotin, TAb, and MMAE in the sample on ATA measurement

The ECL-based ATA measurement has the ability to detect ATA (250 ng/mL) in the presence of brentuximab vedotin 3 μg/mL. The applicant explained that although the impact of TAb which is present in the sample on ATA measurement has not been investigated, TAb is expected to have a similar degree of impact on ATA measurement to that of brentuximab vedotin.

In addition, in the foreign phase II studies (Studies SG035-0003 and SG035-0004) using the proposed dose regimen of brentuximab vedotin, the serum concentrations (median [range]) of brentuximab vedotin and TAb in ATA-negative subjects at ATA measurement points (pre-dose in Cycle 2) were 0.757 [0.09, 1.62] and 1.790 [0.30, 3.59] μg/mL, respectively, in Study SG035-0003, and 0.710 [0.03, 32.70] and 1.745 [0.03, 42.90] μg/mL, respectively, in Study SG035-0004.

Based on the above, the applicant explained as follows:
The ATA measurement was successful for most samples obtained from clinical studies by using ECL assay without interference from brentuximab vedotin and TAb in the sample. In addition, although the impact of MMAE present in the sample on ATA measurement has not been investigated, the plasma concentrations (medians [range]) of MMAE in ATA-negative subjects at the time point of ATA measurement were as low as 0.0876 [0.028, 0.647] in Study SG035-0003 and 0.1435 [0.034, 1.440] ng/mL in Study SG035-0004, MMAE in the sample is unlikely to impact the ATA measurement.

4.(i).A.(3) Impact of soluble CD30 in the sample on measurements of brentuximab vedotin, TAb, and ATA

The impact of soluble CD30 (sCD30) on measurements of brentuximab vedotin (25 ng/mL) and TAb (200 ng/mL) was investigated in the presence of sCD30 (0.01-100 μg/mL). The results showed decreases in measurements of brentuximab vedotin and TAb by >20% in the presence of sCD30 at concentrations of >0.5-fold the serum concentrations of brentuximab vedotin and TAb. In addition, the impact of sCD30 on measurement of ATA (250, 500 ng/mL) was investigated in the presence of sCD30 (0.1-102.4 μg/mL). The results showed that ATA is detectable in the presence of sCD30 even at the highest tested concentration (102.4 μg/mL) although ATA measurements decreased in the presence of sCD30 at concentrations of ≥12.8 μg/mL.

In a foreign phase II study (Study SG035-0003) in patients with Hodgkin's lymphoma (HL), and a foreign phase II study (Study SG035-0004) and the Japanese phase I/II study (Study TB-BC010088) in patients with systemic anaplastic large-cell lymphoma (sALCL, excluding primary cutaneous ALCL limited to the skin), the mean blood sCD30 concentrations at baseline were 0.1562 μg/mL (n = 91; concentration range, 0.012-0.72 μg/mL), 5.7 μg/mL (n = 57; concentration range, 0-154 μg/mL), and 0.404 μg/mL (n = 20; concentration range, 0.0189-3.562 μg/mL), respectively.

Based on the above, the applicant explained the impact of sCD30 in the sample on measurements of brentuximab vedotin, TAb, and ATA as follows:
Regarding the brentuximab vedotin assay and TAb assay, the quantification range is from 0.0125 to 0.4 μg/mL, and sCD30 present in the sample may interfere with these assays. However, binding of sCD30 with brentuximab vedotin may become saturated rapidly after the administration of brentuximab vedotin. Therefore, in actual measurements of clinical samples, serum brentuximab vedotin that can cross-react with CD30 expressed on the cell surface may be assayed. In light of the quantitation range of 0.0125 to 0.4 μg/mL for assays for brentuximab vedotin and TAb and the assumed fast saturation of binding between brentuximab vedotin and sCD30 after administration, the serum concentrations of brentuximab vedotin that can cross-react to CD30 expressed on cell membranes would be determined during the actual clinical sample measurements, in spite of the possible impact of sCD30 in the sample on measurements of brentuximab vedotin and TAb. The ATA measurement is considered possible for most samples obtained from clinical studies without suffering any impact from sCD30 in the samples.

4.(i).A.(4) Changes in manufacturing process for drug substance during development

[redacted].

The comparability of the quality attributes was evaluated at the time of making changes to the manufacturing process (i.e., from Manufacturing process A through Manufacturing process C), which demonstrated the comparability between pre-change and post-change batches of the drug substance.

4.(ii) Summary of clinical pharmacology studies

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

The pharmacokinetics (PK) of brentuximab vedotin was evaluated in patients with CD30-positive haematopoietic malignancies following the administration of brentuximab vedotin alone as well as in combination with ketoconazole or rifampicin.

4.(ii).A.(1) Foreign phase I study (5.3.5.2-1, Study SG035-0001 [November 2006 to July 2009])

An open-label, uncontrolled study was conducted to evaluate the safety and tolerability of brentuximab vedotin in 45 patients with relapsed or refractory CD30-positive haematopoietic malignancies. Brentuximab vedotin was intravenously administered every 3 weeks at a dose of 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.8, 2.7, or 3.6 mg/kg over 2 hours and serum concentrations of brentuximab vedotin and TAb and plasma concentrations of MMAE were determined [the table below]. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

The exposure to brentuximab vedotin was generally dose-proportional over the dose range from 0.1 to 3.6 mg/kg. The applicant explained that the PK of brentuximab vedotin is considered approximately linear over the dose range from 0.1 to 3.6 mg/kg based on the fact that $t_{1/2}$ and CL were generally similar between dose groups of ≥1.2 mg/kg and ≤0.8 mg/kg, although V_{ss} was lower in the ≤0.8 mg/kg groups.

Generally, serum concentrations of brentuximab vedotin peaked immediately after the end of infusion and reached a steady state before Cycle 2. The applicant explained that brentuximab vedotin was suggested to be distributed to blood vessels and intercellular substance based on V_{ss} after administration of 1.2 to 2.7 mg/kg of brentuximab vedotin (approximately 6-10 L) and the reported volumes of plasma (approximately 3 L) and extracellular fluid (approximately 12 L) in human (with a body weight of 60-70 kg) (*Clinical pharmacokinetics: As a basis of clinical pharmacology and medical therapy*, 4th Edition, Nankodo, 2009; *Clinical pharmacokinetics: For appropriate medical therapies*, 2nd Edition, Maruzen, 2007).

The geometric mean ratio [90% confidence interval (CI)] of $AUC_{0\text{-}21d}$ at Cycle 2 or 3 to $AUC_{0\text{-}21d}$ at Cycle 1 in the 1.8 mg/kg group was 1.05 [0.82, 1.34] or 0.93 [0.60, 1.43], respectively, and the geometric mean ratio [90% CI] of C_{max} at Cycle 2 or 3 to C_{max} at Cycle 1 was 1.04 [0.93, 1.17] or 0.73 [0.26, 2.01], respectively, indicating no trend toward accumulation of brentuximab vedotin administered every 3 weeks at a dose of 1.8 mg/kg. However, the geometric mean ratio [90% CI] of $AUC_{0\text{-}21d}$ at Cycle 2 or 3 to $AUC_{0\text{-}21d}$ at Cycle 1 in the 2.7 mg/kg group was 1.12 [1.03, 1.21] or 1.24 [1.10, 1.40], respectively, and the geometric mean ratio [90% CI] of C_{max} at Cycle 2 or 3 to C_{max} at Cycle 1 was 1.08 [0.96, 1.20] or 1.11 [0.96, 1.29], respectively, indicating a trend towards slight accumulation of brentuximab vedotin administered every 3 weeks at a dose of 2.7 mg/kg. The applicant explained that accumulation of brentuximab vedotin was not evaluated in patients in the dose groups other than the 1.8 and 2.7 mg/kg groups because of the limited number of enrolled patients in these groups.

The exposure to MMAE after administration of brentuximab vedotin was generally dose-proportional, and plasma concentrations of MMAE reached a steady state at Cycle 2. $AUC_{0\text{-}21d}$ and C_{max} of MMAE at Cycles 2 and 3 were lower than those at Cycle 1. Although the definite

mechanism of the decrease in the exposure to MMAE after multiple doses of brentuximab vedotin is unknown, a part of MMAE detected in the circulation after administration of brentuximab vedotin might include molecules released as free MMAE upon tumor apoptosis of CD30-expressing cells that internalized brentuximab vedotin. Based on the above, the applicant explained that the reason why the exposure to MMAE decreased with increasing the number of doses of brentuximab vedotin may be that MMAE released from CD30-expressing cells into the circulation decreased due to a decrease in the number of circulating CD30-expressing cells resulting from administration of brentuximab vedotin.

T_{max} was similar between TAb and brentuximab vedotin at any dose, but the exposure to TAb was higher than that to brentuximab vedotin.

PK parameters of brentuximab vedotin and TAb

	Dose (mg/kg)	Cycle	n	$AUC_{0-\infty}$ (day·μg/mL)	AUC_{0-21d} (day·μg/mL)	C_{max} (μg/mL)	T_{max}[*1] (day)	$T_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
Brentuximab vedotin	0.1	1	3	5.36 (42)	5.33 (42)	1.80 (55)	0.083 (0.083, 0.086)	2.38 (25)	1.33 (38)	1.88 (25)
		2	2	-	7.52	2.25	0.098 (0.083, 0.113)	3.10	0.99	1.21
	0.2	1	4	9.82 (6)	9.73 (5)	2.88 (9)	0.085 (0.083, 0.085)	2.47 (74)	1.45 (25)	1.48 (78)
		2	3	-	7.93[*2]	2.45 (13)	0.097 (0.083, 0.656)	2.36[*2]	1.51[*2]	1.79[*2]
	0.4	1	3	22.61 (41)	21.83 (40)	6.14 (36)	0.097 (0.080, 0.115)	5.85 (26)	1.29 (49)	3.66 (76)
		2	3	-	32.42 (31)	8.02 (25)	0.097 (0.085, 0.210)	4.56 (51)	0.89 (34)	1.83 (23)
	0.6	1	3	43.74 (32)	43.13 (32)	10.18 (6)	0.085 (0.084, 0.087)	3.41 (66)	1.10 (49)	1.59 (115)
		2	3	-	43.81 (26)	9.41 (6)	0.087 (0.085, 0.201)	3.30 (28)	1.08 (42)	1.25 (37)
	0.8	1	3	65.59 (40)	64.17 (43)	13.72 (16)	0.090 (0.085, 0.101)	3.79 (63)	1.02 (29)	1.88 (124)
		2	3	-	43.42 (51)	13.06 (23)	0.090 (0.087, 0.091)	3.35 (229)	1.51 (51)	1.49 (165)
	1.2	1	4	46.14 (62)	45.21 (63)	18.89 (27)	0.085 (0.081, 0.092)	3.79 (11)	1.96 (105)	5.85 (260)
		2	5[*3]	-	39.61 (39)	23.03 (20)	0.085 (0.083, 0.093)	5.37 (28)	2.15 (48)	9.32 (32)
	1.8	1	12	79.41 (30)	76.65 (31)	31.98 (29)	0.089 (0.084, 0.254)	4.43 (38)	1.76 (17)	8.21 (24)
		2	11	-	77.58 (44)[*4]	31.67 (17)[*4]	0.090 (0.082, 0.265)[*4]	4.60 (44)[*4]	1.71 (42)[*4]	6.50 (80)[*4]
	2.7	1	12	125.75 (19)	116.94 (20)	45.01 (16)	0.094 (0.087, 0.179)	5.98 (30)	1.71 (33)	10.18 (39)
		2	10	-	128.05 (23)	49.60 (17)	0.090 (0.083, 0.165)	7.84 (52)	1.46 (42)	10.94 (62)
	3.6	1	1	190.71	190.33	76.70	0.115	2.38	1.81	3.88
		2	0	-	-	-	-	-	-	-
TAb	0.1	1	3	-	8.23 (51)	2.33 (72)	0.083 (0.083, 0.086)	-	-	-
		2	2	-	8.01	3.20	0.098 (0.083, 0.113)	-	-	-
	0.2	1	4	-	14.80 (17)	3.51 (11)	0.085 (0.085, 0.210)	-	-	-
		2	3	-	10.93[*5]	3.05 (21)	0.208 (0.097, 0.656)	-	-	-
	0.4	1	3	-	38.96 (48)	7.89 (38)	0.115 (0.080, 0.222)	-	-	-

	Dose (mg/kg)	Cycle	n	$AUC_{0-\infty}$ (day·μg/mL)	AUC_{0-21d} (day·μg/mL)	C_{max} (μg/mL)	T_{max} [*1] (day)	$T_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
		2	3	-	51.01 (34)	9.61 (28)	0.097 (0.085, 0.210)	-	-	-
	0.6	1	3	-	66.38 (15)	14.81 (14)	0.085 (0.084, 0.087)	-	-	-
		2	3	-	59.06 (33)	10.92 (15)	0.201 (0.087, 0.209)	-	-	-
	0.8	1	3	-	85.48 (20)	17.18 (16)	0.101 (0.085, 0.201)	-	-	-
		2	3	-	61.80 (69)	14.24 (23)	0.091 (0.090, 0.208)	-	-	-
	1.2	1	4	-	112.04 (27)	24.67 (26)	0.131 (0.081, 0.247)	-	-	-
		2	5[*3]	-	105.72 (23)	31.91 (26)	0.085 (0.083, 0.176)	-	-	-
	1.8	1	12	-	169.12 (29)	36.63 (28)	0.132 (0.084, 1.103)	-	-	-
		2	11	-	166.61 (51)[*4]	39.69 (35)[*4]	0.091 (0.083, 0.265)[*4]	-	-	-
	2.7	1	12	-	243.46 (22)	53.29 (21)	0.094 (0.087, 0.758)	-	-	-
		2	10	-	282.51 (24)	56.01 (21)	0.092 (0.090, 1.066)	-	-	-
	3.6	1	1	-	441.25	105	0.115	-	-	-
		2	0	-	-	-	-	-	-	-

Geometric mean (coefficient of variation [CV] %); *1, Median (range); *2, n = 1; *3, Including 1 subject who received 1.8 mg/kg at Cycle 1 and received 1.2 mg/kg at Cycle 2, *4, n = 10; *5, n = 2

PK parameters of MMAE

Dose (mg/kg)	Cycle	n	$AUC_{0-\infty}$ (day·ng/mL)	AUC_{0-21d} (day·ng/mL)	C_{max} (ng/mL)	T_{max} [*1] (day)	$T_{1/2}$ (day)
0.1	1	3	2.76[*2]	2.71[*2]	0.27 (10)	5.935 (0.208, 5.944)	4.44[*2]
	2	2	-	-	0.17	6.418 (5.965, 6.870)	-
0.2	1	4	7.35[*3]	7.15[*3]	0.42 (107)	3.016 (0.208, 8.004)	4.13[*3]
	2	3	-	-	0.33 (77)	6.021 (0.656, 6.972)	-
0.4	1	3	6.43 (7)	6.24 (6)	0.65 (7)	0.212 (0.205, 0.222)	4.08 (24)
	2	3	-	6.19[*3]	0.64 (29)	6.847 (0.208, 6.949)	4.58[*3]
0.6	1	3	5.63 (59)	5.53 (58)	0.61 (32)	0.215 (0.212, 7.955)	3.59 (4)
	2	3	-	-	0.47 (91)	6.912 (0.087, 6.934)	-
0.8	1	3	27.98[*3]	27.05[*3]	1.60 (105)	6.964 (6.944, 7.004)	3.46[*3]
	2	3	-	39.27[*3]	2.93 (305)	6.690 (0.184, 6.837)	2.54[*3]
1.2	1	4	20.29 (212)	20.05 (215)	2.72 (272)	1.069 (0.206, 3.088)	3.13 (28)
	2	5[*6]	-	18.41 (91)	2.42 (82)	2.918 (1.083, 3.076)	3.54 (25)
1.8	1	12	37.03 (47)	36.07 (47)	4.97 (43)	2.093 (1.086, 3.934)	3.60 (25)
	2	11	-	27.52 (70)[*4]	2.55 (125)	2.544 (0.254, 6.983)	3.73 (18)[*4]
2.7	1	12	53.20 (41)[*5]	51.28 (39)[*5]	7.00 (44)	2.988 (1.090, 7.813)	3.43 (22)[*5]
	2	10	-	34.49 (69)	3.86 (62)	2.979 (1.000, 6.812)	4.27 (13)
3.6	1	1	-	-	20.00	3.001	-
	2	0	-	-	-	-	-

Geometric mean (CV%); *1, Median (range); *2, n = 1; *3, n = 2; *4, n = 10; *5, n = 11; *6, Including 1 subject who received 1.8 mg/kg at Cycle 1 and received 1.2 mg/kg at Cycle 2.

4.(ii).A.(2) Foreign phase I study (5.3.5.2-2, Study SG035-0002 [March 2008 to February 2010])

An open-label, uncontrolled study was conducted to evaluate the safety and tolerability of brentuximab vedotin in 44 patients with relapsed or refractory CD30-positive haematopoietic malignancies. One treatment cycle consisted of 4 weeks. Brentuximab vedotin was intravenously administered at a dose of 0.4, 0.6, 0.8, 1.0, 1.2, or 1.4 mg/kg on Days 1, 8, and 15 of each cycle, and serum concentrations of brentuximab vedotin and TAb and plasma concentrations of MMAE were determined [the table below]. The infusion duration was 2 hours at the start of the study, but changed to ≥30 minutes in the course of the study. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

The exposures to brentuximab vedotin and MMAE were generally dose-proportional over the dose range from 0.4 to 1.4 mg/kg. Regarding the PK of brentuximab vedotin, the geometric mean ratio [90% CI] of $AUC_{0\text{-}7d}$ in Cycle 3 to $AUC_{0\text{-}7d}$ in Cycle 1 was 1.72 [1.53, 1.94] and 1.28 [0.97, 1.67], respectively, and the geometric mean ratio [90% CI] of C_{max} in Cycle 3 to C_{max} in Cycle 1 was 1.20 [1.10, 1.30] and 1.08 [0.96, 1.22], respectively, indicating a trend towards accumulation of brentuximab vedotin after multiple doses. Regarding the PK of MMAE, the geometric mean ratio [90% CI] of $AUC_{0\text{-}7d}$ in Cycle 3 to $AUC_{0\text{-}7d}$ in Cycle 1 in the 1.0 and 1.2 mg/kg groups was 1.09 [0.66, 1.80] and 1.17 [0.92, 1.49], respectively, and the geometric mean ratio [90% CI] of C_{max} in Cycle 3 to C_{max} in Cycle 1 was 1.05 [0.62, 1.79] and 1.06 [0.84, 1.34], respectively, indicating a slight accumulation after multiple doses.

T_{max} was similar between TAb and brentuximab vedotin at any dose, but the exposure to TAb was higher than that to brentuximab vedotin.

PK parameters of brentuximab vedotin and TAb after administration of brentuximab vedotin

	Dose (mg/kg)	Cycle	n	$AUC_{0\text{-}7d}$ (day·μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	T_{max}*1 (day)
Brentuximab vedotin	0.4	1	4	10.84 (17)	6.56 (10)	0.37 (58)*2	0.09 (0.09, 0.10)
		3	4	20.47 (42)*2	11.78 (18)*2	0.08*3	0.10 (0.09, 0.10)*2
	0.6	1	4	18.69 (23)	11.06 (18)	0.48 (45)	0.09 (0.03, 0.10)
		3	3	12.57 (116)	9.87 (26)	0.32*3	0.10 (0.09, 0.10)
	0.8	1	6	23.70 (31)	13.08 (22)	0.64 (53)*4	0.09 (0.09, 0.16)
		3	5	31.57 (33)	15.83 (23)	0.94 (35)*5	0.10 (0.09, 0.26)
	1.0	1	12	34.54 (13)	21.99 (13)	1.19 (42)*6	0.09 (0.03, 0.25)
		3	9	57.75 (26)	25.65 (27)	2.03 (43)*7	0.09 (0.03, 0.17)
	1.2	1	12	40.19 (8)	24.21 (17)	1.01 (166)*6	0.03 (0.03, 0.11)
		3	7	52.59 (33)*8	26.00 (28)*8	1.76 (47)*4	0.03 (0.02, 0.11)*8
	1.4	1	6	47.00 (21)	28.40 (22)	1.76 (50)*4	0.03 (0.03, 0.10)
		3	5	68.99 (22)*5	27.18 (9)*5	2.37 (29)*5	0.03 (0.03, 0.11)*5
TAb	0.4	1	4	18.18 (28)	7.38 (30)	0.97 (37)*2	0.13 (0.09, 0.20)
		3	4	31.95 (51)*2	9.72 (11)*2	0.23*3	0.10 (0.09, 0.10)*2
	0.6	1	4	28.99 (17)	11.62 (19)	1.05 (32)	0.12 (0.03, 0.18)
		3	3	48.80*3	15.26*3	0.99*3	0.10*3
	0.8	1	6	40.76 (41)	15.86 (33)	1.83 (38)*4	0.09 (0.09, 0.09)
		3	4	75.19 (25)	24.70 (34)	2.58 (53)	0.10 (0.09, 0.25)
	1.0	1	11	60.96 (27)	21.17 (23)	3.61 (51)	0.09 (0.03, 0.25)
		3	9	117.77 (28)	32.69 (26)	5.26 (43)*8	0.10 (0.03, 0.25)
	1.2	1	12	75.00 (19)	27.39 (24)	1.63 (327)*9	0.03 (0.03, 0.20)
		3	6	119.01 (31)*4	38.10 (14)*4	5.43 (37)*4	0.11 (0.03, 0.11)*4
	1.4	1	5	78.08 (27)	26.05 (21)	4.65 (37)	0.03 (0.03, 0.19)
		3	5	143.14 (16)*5	39.32 (21)*5	5.83 (29)*5	0.03 (0.03, 0.03)*5

Geometric mean (CV%); *1, Median (range); *2, n = 3; *3, n = 2; *4, n = 5; *5, n = 4; *6, n = 11; *7, n = 7; *8, n = 6; *9, n = 10

PK parameters of MMAE after administration of brentuximab vedotin

Dose (mg/kg)	Cycle	n	$AUC_{0\text{-}7d}$ (day·ng/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)	T_{max}[*1] (day)
0.4	1	4	8.48 (22)	1.85 (15)	0.13 (194)	1.03 (0.99, 1.07)
	3	4	8.00 (79)	1.71 (72)	0.06 (16)[*2]	0.95 (0.26, 1.04)
0.6	1	4	9.63 (41)	1.91 (39)	0.28 (85)	3.03 (1.03, 3.06)
	3	3	9.25 (53)	1.92 (52)	0.19 (84)	1.01 (0.99, 1.02)
0.8	1	6	8.22 (92)	1.64 (90)	0.16 (45)	2.97 (1.00, 3.00)
	3	5	9.01 (37)	1.74 (39)	0.15 (118)[*3]	1.03 (0.99, 2.99)
1.0	1	12	14.52 (70)	2.78 (77)	0.32 (80)[*4]	2.99 (0.99, 3.06)
	3	9	13.60 (74)	2.56 (72)	0.27 (43)[*5]	0.97 (0.25, 3.01)
1.2	1	12	15.93 (60)	3.12 (60)	0.28 (148)	2.89 (1.00, 3.08)
	3	7	19.48 (32)[*6]	3.51 (33)	0.47 (25)[*7]	1.99 (0.99, 3.07)
1.4	1	5	14.69 (50)	2.97 (56)	0.33 (74)	2.96 (0.98, 3.03)
	3	5	12.83 (51)[*3]	2.62 (45)	0.51 (123)[*3]	1.08 (0.97, 2.99)

Geometric mean (CV%); *1, Median (range); *2, n = 3; *3, n = 4; *4, n = 11; *5, n = 7; *6, n = 6; *7, n = 5

4.(ii).A.(3) Japanese phase I/II study (5.3.5.2-5, Study TB-BC010088 [October 2011 to ongoing (data cutoff date, September 24, 2012)])

An open-label, uncontrolled study was conducted to evaluate the tolerability, safety, and efficacy of brentuximab vedotin in 20 patients with relapsed or refractory CD30-positive HL and sALCL.

In the phase I part, brentuximab vedotin was intravenously administered every 3 weeks at a dose of 1.2 or 1.8 mg/kg, and serum concentrations of brentuximab vedotin and TAb and plasma concentrations of MMAE were determined [the table below]. The infusion duration was 2 hours in Cycles 1 and 2, but was allowed to be reduced to 30 minutes at shortest from Cycle 3 as long as no infusion-related toxicity occurred. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

C_{max} and AUC of brentuximab vedotin were generally dose-proportional across the 1.2 and 1.8 mg/kg groups, and no clear differences were observed in $t_{1/2}$, CL, and V_{ss} between the two groups. Generally, serum concentrations of brentuximab vedotin were highest immediately after the end of infusion. The geometric mean ratio [90% CI] of Cycle 2 to Cycle 1 was 1.12 [0.85, 1.48] for $AUC_{0\text{-}21d}$ and 1.08 [0.91, 1.27] for C_{max} in the 1.2 mg/kg group, and 1.07 [0.84, 1.36] for $AUC_{0\text{-}21d}$ and 0.94 [0.75, 1.19] for C_{max} in the 1.8 mg/kg group, indicating no trend towards accumulation of brentuximab vedotin after multiple doses in either groups.

C_{max} and AUC of MMAE did not increase with increasing dose of brentuximab vedotin. The applicant explained that the reason for this was considered to be the higher exposure to MMAE in 1 subject than in the other 2 subjects in the 1.2 mg/kg group, but that the definite reason for the patient's high exposure was unknown. In addition, the geometric mean ratio [90% CI] of Cycle 2 to Cycle 1 was 0.66 [0.42, 1.06] for $AUC_{0\text{-}21d}$ and 0.53 [0.29, 0.95] for C_{max} in the 1.2 mg/kg group and 0.69 [0.33, 1.41] for $AUC_{0\text{-}21d}$ and 0.52 [0.21, 1.29] for C_{max} in the 1.8 mg/kg groups, indicating a tendency for exposure to MMAE to decrease after multiple doses.

T_{max} was similar between TAb and brentuximab vedotin at any dose, but the exposure to TAb was higher than that of brentuximab vedotin.

PK parameters of brentuximab vedotin and TAb after administration of brentuximab vedotin

	Dose (mg/kg)	Cycle	$AUC_{0-\infty}$ (day·μg/mL)	AUC_{0-21d} (day·μg/mL)	C_{max} (μg/mL)	T_{max}* (day)	$T_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
Brentuximab vedotin	1.2	1	41.96 (31.67)	40.17 (29)	18.89 (34)	0.090 (0.087, 0.228)	4.94 (41)	1.40 (38)	7.16 (24)
		2	-	44.94 (47.09)	20.31 (40.46)	0.088 (0.083, 0.169)	5.06 (65)	1.30 (51)	6.87 (17)
	1.8	1	74.23 (5.702)	66.76 (1.5)	31.47 (9.6)	0.089 (0.088, 0.094)	7.42 (49)	1.20 (16)	8.85 (26)
		2	-	71.42 (13)	29.60 (13)	0.174 (0.167, 0.240)	7.29 (13)	1.25 (24)	9.58 (11)
TAb	1.2	1	-	79.04 (31)	21.94 (24)	0.087 (0.082, 0.090)	-	-	-
		2	-	84.44 (45)	20.34 (33)	0.088 (0.083, 0.249)	-	-	-
	1.8	1	-	145.5 (4.5)	34.78 (14)	0.089 (0.088, 0.094)	-	-	-
		2	-	155.2 (7.4)	35.75 (15)	0.174 (0.094, 0.240)	-	-	-

Geometric mean (CV%); n = 3; *, Median (range)

PK parameters of MMAE after administration of brentuximab vedotin

Dose (mg/kg)	Cycle	$AUC_{0-\infty}$ (day·ng/mL)	AUC_{0-21d} (day·ng/mL)	C_{max} (ng/mL)	T_{max}* (day)	$T_{1/2}$ (day)
1.2	1	27.66 (65.59)	27.19 (65)	4.16 (73)	2.92 (1.07, 3.94)	3.57 (12)
	2	-	18.00 (107)	2.20 (123)	2.93 (1.10, 2.98)	3.71 (15)
1.8	1	23.30 (42.13)	22.78 (43)	3.59 (50)	1.97 (1.95, 3.96)	3.57 (12)
	2	-	15.67 (7.5)	1.86 (8.4)	2.96 (1.04, 2.98)	4.15 (11)

Geometric mean (CV%); n = 3; *, Median (range)

4.(ii).A.(4) Foreign phase I study (5.3.3.4-1, Study SGN35-008A [December 2009 to June 2010])

An open-label study was conducted to evaluate the effect of brentuximab vedotin on the PK of a CYP3A4 substrate (midazolam) (A-mid group), the effect of a CYP3A4 inducer (rifampicin) on the PK of brentuximab vedotin and MMAE (A-rif group), the effect of a CYP3A4 inhibitor (ketoconazole) on the PK of brentuximab vedotin and MMAE (A-ket group), and the mass balance of MMAE in 56 patients (45 patients included in PK analysis) with relapsed or refractory CD30-positive haematopoietic malignancies. One treatment cycle consisted of 3 weeks. Brentuximab vedotin was to be administered at a dose of 1.2 mg/kg (A-ket group) or 1.8 mg/kg (groups other than the A-ket group) on Day 1 of each cycle. In the A-mid group, 1 mg of midazolam was to be intravenously administered 3 days before Cycle 1 and on Day 3 of Cycle 1. In the A-rif group, 600 mg of rifampicin was to be orally administered once daily from Day 14 of Cycle 1 to Day 21 of Cycle 2. In the A-ket group, 400 mg of ketoconazole was to be orally administered once daily from Day 19 of Cycle 1 to Day 21 of Cycle 2. The mass balance of MMAE was evaluated in the A-rif group. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

The PK parameters of midazolam in the A-mid group were as shown in the table below. The 90% CI of the geometric mean ratio for midazolam $AUC_{0-\infty}$ (concomitant use with brentuximab vedotin vs. midazolam alone) fell within the criterion for bioequivalence (0.80-1.25). However, the 90% CI of the geometric mean ratio for midazolam C_{max} (concomitant use with brentuximab vedotin vs. midazolam alone) exceeded both the upper and lower limits of the criterion for bioequivalence.

The applicant explained the results as follows:
Blood midazolam concentrations have been reported to rapidly decrease during the distribution phase (*Japanese Journal of Clinical Pharmacology and Therapeutics*. 1983;14:573-91) and the measurement values may have substantially varied due to slight variation in the blood sampling time point. Therefore, it is difficult to discuss the possibility of pharmacokinetic interactions between midazolam and brentuximab vedotin or MMAE based on the data of C_{max}. However, taking into account that the geometric mean ratio for C_{max} is approximately 1 and that no effects of the concomitant use with brentuximab vedotin were observed on $AUC_{0\text{-}inf}$, pharmacokinetic interactions between CYP3A4 substrates and brentuximab vedotin or MMAE are unlikely to occur in clinical settings.

PK parameters of midazolam in the A-mid group

	n	Midazolam alone	Concomitant use with brentuximab vedotin	Geometric mean ratio [90% CI]
$AUC_{0\text{-}inf}$ (hr·μg/mL)	15	0.079	0.074	0.94 [0.81, 1.10]
C_{max} (μg/mL)	14	0.073	0.084	1.15 [0.76, 1.74]

Geometric mean

The PK parameters of brentuximab vedotin and MMAE in the A-rif group were as shown in the table below. The 90% CIs of the geometric mean ratio for $AUC_{0\text{-}\infty}$ and C_{max} of brentuximab vedotin (concomitant use with rifampicin vs. brentuximab vedotin alone) fell within the criterion for bioequivalence (0.8-1.25). However, the upper limits of the 90% CI of the corresponding geometric mean ratio for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}10d}$, and C_{max} of MMAE were <1, indicating a tendency for exposure to MMAE to decrease with concomitant use of brentuximab vedotin with rifampicin.

The applicant explained the results as follows:
Tumor response to brentuximab vedotin was suggested to be more strongly related to exposure to brentuximab vedotin than to that to MMAE [see "4.(ii).A.(8).1) Relationship between exposure and efficacy"] and a low exposure to MMAE is unlikely to substantially diminish the efficacy of brentuximab vedotin. In addition, adverse events such as neutropenia have been suggested to be related to a high exposure to MMAE [see "4.(ii).A.(8).2) Relationship between exposure and safety"], and the risk of adverse events is not considered to increase with decreasing exposure to MMAE. Based on the above, there is less need to provide a caution about pharmacokinetic interactions between CYP3A4 inducers and brentuximab vedotin.

PK parameters of brentuximab vedotin and MMAE in the A-rif group

	PK parameter	n	Brentuximab vedotin alone	Concomitant use with rifampicin	Geometric mean ratio [90% CI]
Brentuximab vedotin	$AUC_{0\text{-}\infty}$ (day·μg/mL)	11	89.84	93.40	1.04 [0.87, 1.24]
	C_{max} (μg/mL)	11	36.74	34.05	0.93 [0.81, 1.06]
MMAE	$AUC_{0\text{-}\infty}$ (day·ng/mL)	14	40.06	21.54	0.54 [0.43, 0.68]
	$AUC_{0\text{-}10d}$ (day·ng/mL)	14	31.83	17.66	0.55 [0.44, 0.71]
	C_{max} (ng/mL)	14	4.98	2.80	0.56 [0.42, 0.76]

Geometric mean

The PK parameters of brentuximab vedotin and MMAE in the A-ket group were as shown in the table below. The 90% CI of the geometric mean ratio for $AUC_{0\text{-}\infty}$ of brentuximab vedotin (concomitant use with ketoconazole vs. brentuximab vedotin alone) fell within the criterion for bioequivalence (0.8-1.25), but the 90% CI of the corresponding geometric mean ratio for C_{max} exceeded both the upper and lower limits of the criterion for bioequivalence, with a large interindividual variability. The applicant explained that, in spite of the above, ketoconazole was not considered to have an apparent effect on the PK of brentuximab vedotin given that the

geometric mean ratios for $AUC_{0-\infty}$ and C_{max} of brentuximab vedotin were both approximately 1. Regarding MMAE, however, the applicant explained that the possibility was suggested that the exposure to MMAE may increase with concomitant use of brentuximab vedotin with ketoconazole because the upper limits of the 90% CI of the geometric mean ratios for $AUC_{0-\infty}$, AUC_{0-17d}, and C_{max} (concomitant use with ketoconazole vs. brentuximab vedotin alone) exceeded 1.

PK parameters of brentuximab vedotin and MMAE in the A-ket group

	PK parameter	n	Brentuximab vedotin alone	Concomitant use with ketoconazole	Geometric mean ratio [90% CI]
Brentuximab vedotin	$AUC_{0-\infty}$ (day·μg/mL)	11	52.77	56.26	1.07 [0.95, 1.19]
	C_{max} (μg/mL)	16	22.57	22.38	0.99 [0.75, 1.31]
MMAE	$AUC_{0-\infty}$ (day·ng/mL)	14	26.65	35.72	1.34 [0.98, 1.84]
	AUC_{0-17d} (day·ng/mL)	14	25.82	32.05	1.24 [0.95, 1.61]
	C_{max} (ng/mL)	16	4.11	5.13	1.25 [0.90, 1.72]

Geometric mean

The mass balance of MMAE was evaluated in 8 subjects in the A-rif group. As a result, approximately 23.5% of the administered dose was recovered as MMAE in urine and feces within 1 week after administration of brentuximab vedotin and 72% of the recovered MMAE was excreted in feces. MMAE was mainly excreted as an unchanged compound in urine and feces, and an additional 8 compounds were excreted as metabolites of MMAE in urine and feces. The applicant explained that the above findings suggested that MMAE is mainly excreted as an unchanged compound in feces in humans.

4.(ii).A.(5) Foreign phase I study (5.3.5.4-1, Study SGN35-007 [February 2010 to August 2011])

An open-label, uncontrolled study was conducted to evaluate the effects of brentuximab vedotin on ventricular repolarization in 52 patients (46 patients in analysis) with relapsed or refractory CD30-positive haematopoietic malignancies. Brentuximab vedotin was intravenously administered every 3 weeks at a dose of 1.8 mg/kg over 30 minutes, and serum concentrations of brentuximab vedotin and TAb, plasma concentrations of MMAE, and electrocardiogram were evaluated. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

The applicant explained that since the upper limit of the 90% CI of the mean change in QTcF interval was <10 msec at any observation points, administration of brentuximab vedotin at the proposed dose regimen was unlikely to cause clinically significant QTcF interval prolongation in patients with CD30-positive haematopoietic malignancies. In addition, based on the significant relation between the plasma MMAE concentrations at Cycles 1 and 3 and the change in QTcF interval from baseline, MMAE at a plasma concentration of 7.0 ng/mL, which is equivalent to C_{max} of MMAE after administration of 1.8 mg/kg of brentuximab vedotin, was expected to lead to change in QTcF interval of -6.5 msec. The applicant explained that, in spite of the above, the QTc shortening obtained from the simulation results was small in extent and considered unrelated to the safety risk and that the QTc change observed in Study SGN35-007 was not be clinically significant.

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

A population pharmacokinetic (PPK) analysis of brentuximab vedotin and MMAE was conducted using nonlinear mixed-effect model based on PK data obtained from 314 patients with relapsed or refractory CD30-positive haematopoietic malignancies (7081 time points and 7452 time points

for brentuximab vedotin and MMAE, respectively) in the following 6 studies: foreign phase I studies (Studies SG035-0001, SG035-0002, SGN35-008A, and SGN35-008B [only data from 4 subjects available at present were included in this analysis; see "4.(ii).A.(7) Effects of function kidney decreased and function liver decreased on PK of brentuximab vedotin and MMAE"]) and foreign phase II studies (Studies SG035-0003 and SG035-0004). The PK of brentuximab vedotin was described by a 3-compartment model assuming 2 formation pathways of MMAE as the routes of elimination of brentuximab vedotin (One in which MMAE is formed directly from brentuximab vedotin and the other in which MMAE is formed from target-bound brentuximab vedotin), and the PK of MMAE was described by a 2-compartment model. As covariates on PK parameters (CL, V_c) of brentuximab vedotin and MMAE, the following parameters were investigated: sex, age, race, ethnicity, body weight, body surface area, disease (HL, sALCL, others), creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin levels, immunogenicity, dose, treatment cycle, baseline tumor size, and manufacturing process. As a result, body weight was identified as a clinically significant covariate on PK parameters of brentuximab vedotin (CL, V_c) and MMAE (V_c), and these parameters were found to be high in patients with high body weight.

The applicant explained that, based on the above, it is appropriate to define the dose of brentuximab vedotin according to body weight (1.8 mg/kg).

In clinical studies of brentuximab vedotin, the dose for patients weighing >100 kg at baseline was to be calculated by assuming a body weight of 100 kg; the applicant explained that this was appropriate for the following reasons:

- The exposures to brentuximab vedotin in patients with a baseline body weight of >100 kg who were enrolled in the foreign phase II studies (11 patients in Study SG035-0003, 7 patients in Study SG035-0004) fell within the range of those in patients with a baseline body weight of 70 kg.

- A subgroup analysis of efficacy and safety data from Studies SG035-0003 and SG035-0004 according to the baseline body weight showed no clear differences in the efficacy and safety of brentuximab vedotin between patients with a baseline body weight of >100 kg and those with ≤100 kg.

4.(ii).A.(7) Effects of function kidney decreased and function liver decreased on PK of brentuximab vedotin and MMAE

The applicant explained the need to adjust the dose of brentuximab vedotin in patients with renal impairment or hepatic impairment and to provide relevant cautions as follows:
Although no clinical study data evaluating the PK of brentuximab vedotin and MMAE in patients with renal impairment or hepatic impairment have been available, a PPK analysis was conducted to explore the PK of brentuximab vedotin and MMAE in those patients.

Regarding patients with renal impairment, results of an analysis in patients with low creatinine clearance suggested that CL of brentuximab vedotin is affected by severe function kidney decreased (creatinine clearance <30 mL/min) and that CL of MMAE is affected by moderate or severe function kidney decreased (creatinine clearance ≤50 mL/min). Although these analysis results indicated that exposures to brentuximab vedotin and MMAE may increase in patients with severe renal impairment, it is difficult to derive a definitive conclusion on the effects of renal impairment on the PK of brentuximab vedotin and MMAE, taking account of the limited number of patients with moderate and severe renal impairment enrolled in the clinical studies analyzed (8 patients and 3 patients, respectively). Regarding patients with hepatic impairment, an analysis was conducted using ALT, AST, total bilirubin, and serum albumin levels as indexes of liver function. As a result, no clear association with the PK of brentuximab vedotin and MMAE was

shown for either index. Based on the above, there is little need to adjust the dose of brentuximab vedotin in patients with renal impairment or hepatic impairment and to provide relevant cautions.

A foreign phase I study (Study SGN35-008B) is ongoing to evaluate the effects of function kidney decreased and function liver decreased on the PK of brentuximab vedotin and MMAE, and results of the study will be available after [redacted] 20[redacted].

4.(ii).A.(8) Relationship between exposure and efficacy or safety

4.(ii).A.(8).1) Relationship between exposure and efficacy

Based on the results of foreign phase I studies in patients with CD30-positive haematopoietic malignancies (Study SG035-0001 [brentuximab vedotin at doses of 0.1-3.6 mg/kg administered once every 3 weeks], Study SG035-0002 [brentuximab vedotin at doses of 0.4-1.4 mg/kg administered once a week]), the relationship between the exposures (AUC, C_{max}) to brentuximab vedotin and MMAE at Cycle 1 and the maximum percent change in tumor volume was investigated. The number of sALCL patients enrolled in Studies SG035-0001 and SG035-0002 was limited (7 patients) and only HL patients were included in this analysis. The results showed that a significant correlation exists between AUC and C_{max} of brentuximab vedotin at Cycle 1 and the maximum tumor reduction in both Studies SG035-0001 and SG035-0002. Regarding MMAE, however, a significant correlation was shown between AUC and C_{max} of MMAE and the maximum tumor reduction in Study SG035-0001, but no significant correlation was shown in Study SG035-0002. The applicant explained that the above findings suggested that tumor response to brentuximab vedotin may correlate more strongly with exposure to brentuximab vedotin than with that to MMAE.

4.(ii).A.(8).2) Relationship between exposure and safety

Based on pooled data from foreign phase I studies (Studies SG035-0001 and SG035-0002) and foreign phase II studies (Studies SG035-0003 and SG035-0004), the relationship between exposures (AUC, C_{max}) to brentuximab vedotin and MMAE at steady state and the severity of adverse events (diarrhoea, neutropenia, neuropathy peripheral) was investigated. As a result, no clear relationship was shown between the severity of diarrhoea and exposures to brentuximab vedotin and MMAE. Neutropenia tended to be severer in patients with higher AUC of brentuximab vedotin and patients with higher AUC and C_{max} of MMAE, and neuropathy peripheral-related events tended to be severer in patients with higher AUC of brentuximab vedotin.

Similar results were found in an analysis of pooled data from the foreign phase II studies (Studies SG035-0003 and SG035-0004) only.

4.(ii).A.(9) Effects of ATA on PK of brentuximab vedotin

Production of ATA after administration of brentuximab vedotin was investigated using ECL assay in Studies SG035-0002, SG035-0003, SG035-0004, SGN35-008A, and TB-BC010088. Among subjects for whom ATA was assayed before and after administration of brentuximab vedotin in Studies SG035-0002, SG035-0003, SG035-0004, SGN35-008A, and TB-BC010088, 3 of 42 subjects (7%), 6 of 101 subjects (6%), 2 of 56 subjects (4%), 6 of 54 subjects (11%), and 3 of 17 subjects (18%) were respectively found to be ATA-positive before administration, and 14 of 42 subjects (33%), 35 of 101 subjects (35%), 22 of 56 subjects (39%), 21 of 54 subjects (39%), and 8 of 17 subjects (47%) were respectively found to be ATA-positive after administration. In addition, in Studies SG035-0002, SG035-0003, SG035-0004, SGN35-008A, and TB-BC010088, 12 of 42 subjects (29%), 30 of 101 subjects (30%), 21 of 56 subjects (38%), 18 of 54 subjects (33%), and 6 of 17 subjects (35%) were respectively negative before administration but converted to positive for the first time after administration of brentuximab vedotin.

The applicant explained the effects of ATA on the PK of brentuximab vedotin as follows:

Based on PK data from Studies SG035-0002, SGN35-008A, and TB-BC010088, the effects of ATA on the PK of brentuximab vedotin were investigated. As a result, the geometric means (CV%) of CL of brentuximab vedotin in ATA-negative and ATA-positive patients were 0.0618 mL/hr (42.4%) in ATA-negative patients (27 of 44 patients) and 0.0812 mL/hr (56.4%) in ATA-positive patients (17 of 44 subjects) in Study SG035-0002; 1.382 mL/hr (43.3%) in ATA-negative patients (23 of 39 patients) and 2.582 mL/hr (79.4%) in ATA-positive patients (16 of 39 subjects) in Study SGN35-008A; and 1.043 mL/hr (21.04%) in ATA-negative patients (3 of 6 patients) and 1.555 mL/hr (36.36%) in ATA-positive patients (3 of 6 subjects) in Study TB-BC010088; the CL of brentuximab vedotin tended to be higher in ATA-positive patients than in ATA-negative patients in all studies. However, at present, the effects of ATA on the PK of brentuximab vedotin are considered unclear taking account of the large interindividual variability in CL observed in all studies and the limited number of subjects included in Study TB-BC010088. Immunogenicity was not found to be a significant covariate for the PK of brentuximab vedotin in the PPK analysis [see "4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"].

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

4.(ii).B.(1) Difference in the PK of brentuximab vedotin between Japanese and foreign subjects

The applicant explained the difference in PK of brentuximab vedotin, MMAE, and TAb between Japanese and foreign subjects as follows:

Based on the results from a Japanese clinical study (Study TB-BC010088) and foreign clinical studies (Studies SG035-0001 and SGN35-008A), in which brentuximab vedotin was intravenously administered every 3 weeks at a dose of 1.2 or 1.8 mg/kg, the difference in the PK of brentuximab vedotin, MMAE, and TAb between Japanese and foreign subjects after administration of brentuximab vedotin was investigated. As a result, C_{max} and AUC of brentuximab vedotin did not differ between Japanese and foreign subjects either after the first dose or second dose, while $t_{1/2}$ tended to be longer and CL tended to be lower in Japanese subjects than in foreign subjects. However, considering the large interindividual variability of CL and $t_{1/2}$ of brentuximab vedotin, it is considered that no clear differences in these parameters have been observed between Japanese and foreign subjects. C_{max} and AUC of MMAE did not differ between Japanese and foreign subjects after administration of brentuximab vedotin at a dose of 1.2 mg/kg, but these parameters tended to be lower in Japanese subjects after administration at a dose of 1.8 mg/kg. The lower C_{max} and AUC of MMAE in Japanese subjects in the 1.8 mg/kg group were considered attributable to the low exposure to MMAE observed in 1 Japanese subject compared with the other 2 subjects, and a large interindividual variability of C_{max} and AUC of MMAE was observed in the foreign clinical studies. Based on these findings, it is considered that no clear differences in the PK of MMAE exist between Japanese and foreign subjects. C_{max} of TAb did not differ between Japanese and foreign subjects, while AUC of TAb tended to be slightly lower in Japanese subjects. Considering the large interindividual variability of AUC of TAb, however, no clear differences in the PK of TAb have been observed between Japanese and foreign subjects.

Based on the above, the applicant considered that no clear differences in the PK of brentuximab vedotin, MMAE, and TAb have been observed between Japanese and foreign subjects after administration of brentuximab vedotin.

PMDA considers as follows:

Given the large interindividual variability of the PK of brentuximab vedotin, MMAE, and TAb after administration of brentuximab vedotin in both Japanese and foreign subjects and the limited number of subjects (6 subjects) included in the PK evaluation in Japanese subjects, although there are limitations to the rigorous evaluation of difference in the PK between Japanese and foreign subjects, at present, no tendency has been observed for the PK of brentuximab vedotin, MMAE, and TAb after administration of brentuximab vedotin to clearly differ between Japanese and foreign subjects. However, currently available data about differences in the PK of brentuximab

vedotin, MMAE, and TAb between Japanese and foreign subjects are limited, thus, it is necessary to continue to collect information that can be used for evaluation of differences in the PK of brentuximab vedotin, MMAE, and TAb between Japanese and foreign subjects and appropriately provide information if a new finding becomes available.

4.(ii).B.(2) Pharmacokinetic interactions

Since non-clinical studies showed that MMAE is a substrate of P-glycoprotein (P-gp) [see "3.(ii).A.(6).3) Transporters"], PMDA asked the applicant to explain the need to provide a caution about concomitant use with P-gp inhibitors or inducers.

The applicant responded as follows:

Since MMAE is a substrate of P-gp, concomitant use with P-gp inhibitors or inducers may affect exposure to MMAE. However, there is less need to provide a caution about pharmacokinetic interactions between P-gp inhibitors or inducers and brentuximab vedotin because these interactions are unlikely to be of clinical relevance for the following reasons:

- Although concomitant use of brentuximab vedotin with P-gp inhibitors may increase the exposure to MMAE, the extent of increase in exposure to MMAE and occurrence of adverse events resulting from P-gp inhibition is not clear at present. In addition, although concomitant use of brentuximab vedotin with P-gp inducers may decrease the exposure to MMAE, this is not considered to increase the risk of adverse events.

- Given the results of the analysis on exposure to MMAE and tumor response after administration of brentuximab vedotin [see "4.(ii).A.(8).1) Relationship between exposure and efficacy"] indicating that the efficacy of brentuximab vedotin is likely to correlate more strongly with exposure to brentuximab vedotin than with that to MMAE, change in exposure to MMAE caused by concomitant use of brentuximab vedotin with P-gp inhibitors or inducers is unlikely to have a clinically relevant effect on the efficacy of brentuximab vedotin.

PMDA considers as follows:

Since pharmacokinetic interactions between P-gp inhibitors or inducers and brentuximab vedotin are unclear, it is necessary to continue to collect information and appropriately provide information if a new finding becomes available about such pharmacokinetic interactions. The fact that MMAE is a substrate of P-gp should be appropriately communicated via the package insert.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from 7 studies including a Japanese phase I/II study, 4 foreign phase I studies, and 2 foreign phase II studies were submitted.

List of clinical studies on efficacy and safety

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoints
Evaluation	Japan	TB-BC010088	I/II	Patients with relapsed or refractory CD30-positive HL or sALCL	Phase I: 6 Phase II: 14	Phase I: Brentuximab vedotin 1.2 or 1.8 mg/kg/dose every 3 weeks Phase II: Brentuximab vedotin 1.8 mg/kg/dose every 3 weeks	Safety Efficacy
	Foreign	SGN35-007	I	Patients with relapsed or refractory CD30-positive haematopoietic malignancies	52	Brentuximab vedotin 1.8 mg/kg/dose every 3 weeks	Safety
		SGN35-008A	I	Patients with relapsed or refractory CD30-positive haematopoietic malignancies	56	Brentuximab vedotin 1.2 or 1.8 mg/kg/dose every 3 weeks	PK
		SG035-0001	I	Patients with relapsed or refractory CD30-positive haematopoietic malignancies	45	Brentuximab vedotin 0.1 to 3.6 mg/kg/dose every 3 weeks	Safety
		SG035-0002	I	Patients with relapsed or refractory CD30-positive haematopoietic malignancies	44	Brentuximab vedotin 0.4 to 1.4 mg/kg/dose every week	Safety
		SG035-0003	II	Patients with relapsed or refractory CD30-positive HL	102	Brentuximab vedotin 1.8 mg/kg/dose every 3 weeks	Safety Efficacy
		SG035-0004	II	Patients with relapsed or refractory CD30-positive sALCL	58	Brentuximab vedotin 1.8 mg/kg/dose every 3 weeks	Safety Efficacy

HL, Hodgkin's lymphoma; sALCL, Systemic anaplastic large cell lymphoma

The individual clinical studies are summarized below.

Major adverse events other than deaths reported in each clinical study are described in "4.(iv) Adverse events, etc. observed in clinical studies," and PK data, etc. in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

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

The results from the following 2 clinical pharmacology studies in patients with CD30-positive haematopoietic malignancies were submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. As death in study or within 30 days after the last dose of the study drug, 1 death due to disease progression was reported in Study SGN35-007. In addition, 1 death was reported due to haemorrhage intracranial/cytomegalovirus infection/pancytopenia in Study SGN35-008A, and a causal relationship to brentuximab vedotin could not be ruled out for all these adverse events.

4.(iii).A.(1).1) Foreign phase I study (5.3.5.4-1, Study SGN35-007 [February 2010 to August 2011])

4.(iii).A.(1).2) Foreign phase I study (5.3.3.4-1, Study SGN35-008A [December 2009 to June 2010])

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

Japanese phase I/II study (5.3.5.2-5, Study TB-BC010088 [October 2011 to ongoing (data cutoff date, September 24, 2012)])

An open-label, uncontrolled study was conducted to evaluate the safety and efficacy of brentuximab vedotin in patients with relapsed or refractory CD30-positive HL and sALCL (target sample size, 17-23) at 3 centers for phase I part and 5 centers for phase II part in Japan.

In the phase I part, brentuximab vedotin was to be intravenously administered every 3 weeks at doses of 1.2 and 1.8 mg/kg. In the phase II part, brentuximab vedotin was to be intravenously administered every 3 weeks at a dose of 1.8 mg/kg/dose. The treatment was allowed to be continued up to 16 cycles unless progressive disease (PD) or intolerable toxicity occurred. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

All of the 20 subjects enrolled into the study received brentuximab vedotin and were included in the safety analysis.

In the phase I part, dose limiting toxicities (DLTs) were to be evaluated in Cycle 1, during which tolerability etc. was assessed. As a result, no DLTs were observed in the 6 enrolled subjects, and maximum tolerated dose (MTD) was not reached. In the phase II part, the primary efficacy endpoint was best overall response determined by central review, and the results are summarized as tumor response in the table below.

Tumor response (central review; data cutoff date, September 24, 2012)

Best overall response*1	Number of subjects (%)	
	HL N = 9	sALCL N = 5
Complete response (CR)	2 (22.2)	2 (40.0)
Partial response (PR)	4 (44.4)	2 (40.0)
Stable disease (SD)	3 (33.3)	0
PD	0	0
Unevaluable/Not evaluated	0	1 (20.0)*2
Number of responders (CR or PR) (response rate [95% CI], %)	6 (66.7 [29.9, 92.5])	4 (80.0 [28.4, 99.5])

*1, Based on Revised Response Criteria for Malignant Lymphoma (*J Clin Oncol.* 2007;25:579-86)
*2, One subject had not yet undergone an imaging evaluation as of the data cutoff date.

Regarding safety, no deaths were reported during the treatment period or follow-up period (up to 28 days after the last dose of brentuximab vedotin).

4.(iii).A.(3) Foreign clinical studies

4.(iii).A.(3).1) Foreign phase I study (5.3.5.2-1, Study SG035-0001 [November 2006 to July 2009])

An open-label, uncontrolled study was conducted to evaluate the safety and MTD of brentuximab vedotin in patients with relapsed or refractory CD30-positive haematopoietic malignancies (target sample size, 42-51 in total or 3-12 subjects for each dose level) at 4 centers overseas.

Brentuximab vedotin was to be intravenously administered every 3 weeks at doses of 0.1, 0.2, 0.4, 0.6, 0.8, 1.2, 1.8, 2.7, or 3.6 mg/kg. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

All of the 45 subjects enrolled into the study received brentuximab vedotin and were included in the safety analysis.

DLTs were to be evaluated in Cycle 1, during which tolerability etc. were assessed. DLTs were observed in 1 of 6 subjects (17%) each in the 1.8 and 2.7 mg/kg cohorts (Grade 4

thrombocytopenia and Grade 3 acute kidney injury, respectively). The only subject who received treatment in the 3.6 mg/kg cohort experienced Grade 5 febrile neutropenia and septic shock after the first dose of brentuximab vedotin and died. Subsequently, 12 patients each in the 1.8 and 2.7 mg/kg cohorts received brentuximab vedotin. No additional DLTs were observed in the 1.8 mg/kg cohort, but additional adverse events that were considered as DLTs (Grade 3 hyperglycaemia, Grade 3 prostatitis, Grade 3 febrile neutropenia) were reported in 2 subjects in the 2.7 mg/kg cohort. Consequently, 3 of 12 subjects (25%) in the 2.7 mg/kg cohort experienced DLTs. Based on the above results, the MTD of brentuximab vedotin was determined to be 1.8 mg/kg.

Regarding safety, death during the treatment period or within 30 days after the last dose was observed in 1 of 1 subject (100%) in the 3.6 mg/kg group. The death of this patient was considered to be caused by febrile neutropenia and septic shock, for which a causal relationship to brentuximab vedotin could not be ruled out.

4.(iii).A.(3).2) Foreign phase I study (5.3.5.2-2, Study SG035-0002 [March 2008 to February 2010])

An open-label, uncontrolled study was conducted to evaluate the safety and MTD of every week dosing of brentuximab vedotin alone and in concomitant use with gemcitabine hydrochloride (gemcitabine) in patients with relapsed or refractory CD30-positive haematopoietic malignancies (target sample size, 39-72 in total or 3-12 subjects for each dose level) at 5 centers overseas.

Brentuximab vedotin was to be intravenously administered at a dose of 0.4, 0.6, 0.8, 1.0, 1.2, or 1.4 mg/kg on Days 1, 8, and 15 in each cycle; one treatment cycle consisted of 4 weeks. The treatment was allowed to be continued up to 12 cycles unless PD or intolerable toxicity occurred. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

All of the 44 subjects enrolled into the study received brentuximab vedotin and were included in the safety analysis.

DLTs were to be evaluated in Cycle 1, during which tolerability etc. was assessed. DLTs were observed in 2 of 12 subjects in the 1.0 mg/kg cohort (Grade 3 diarrhoea, Grade 3 vomiting) and in 2 of 6 subjects in the 1.4 mg/kg cohort (Grade 3 diarrhoea, Grade 4 hyperglycaemia). This study was originally planned to start enrollment into the combination therapy with gemcitabine after the completion of enrollment into the monotherapy, but terminated early at the discretion of the applicant at the end of the monotherapy; the safety etc. of concomitant use of brentuximab vedotin with gemcitabine was not evaluated.

Regarding safety, death during the treatment period or within 30 days after the last dose was observed in 1 of 12 subjects (8.3%) in the 1.2 mg/kg group. The death of this patient was considered to be caused by pneumonia influenzal, for which a causal relationship to brentuximab vedotin was ruled out.

4.(iii).A.(3).3) Foreign phase II study (5.3.5.2-3, Study SG035-0003 [February 2009 to August 2010])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory HL who had undergone autologous haematopoietic stem cell transplantation (ASCT) (target sample size, 100) at 25 centers overseas.

Brentuximab vedotin was to be intravenously administered every 3 weeks at a dose of 1.8 mg/kg. The treatment was allowed to be continued up to 16 cycles unless PD or intolerable toxicity

occurred. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

All of the 102 subjects enrolled into the study received brentuximab vedotin and were included in the efficacy and safety analyses.

The primary efficacy endpoint was best overall response determined by central review, and the results are summarized as tumor response in the table below.

Tumor response (central review, total patient population, N = 102)

Best overall response*	Number of subjects (%)
CR	34 (33.3)
PR	42 (41.2)
SD	22 (21.6)
PD	3 (2.9)
Unevaluable/Not evaluated	1 (1.0)
Number of responders (CR or PR) (response rate [95% CI], %)	76 (74.5 [64.9, 82.6])

* Based on "Revised Response Criteria for Malignant Lymphoma" (*J Clin Oncol*. 2007;25:579-86)

Regarding safety, no deaths were reported during the treatment period or within 30 days after the last dose.

4.(iii).A.(3).4) Foreign phase II study (5.3.5.2-4, Study SG035-0004 [June 2009 to June 2011])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of brentuximab vedotin in patients with relapsed or refractory sALCL who had received a combination treatment of cyclophosphamide hydrate, doxorubicin hydrochloride (doxorubicin), vincristine sulfate (vincristine), and prednisolone or an equivalent chemotherapy regimen (target sample size, 55) at 22 centers overseas.

Brentuximab vedotin was to be intravenously administered every 3 weeks at a dose of 1.8 mg/kg. The treatment was allowed to be continued up to 16 cycles unless PD or intolerable toxicity occurred. For patients weighing >100 kg at baseline, the dose was calculated by assuming a body weight of 100 kg.

All of the 58 subjects enrolled into the study received brentuximab vedotin and were included in the efficacy and safety analyses.

The primary efficacy endpoint was best overall response determined by central review, and the results are summarized as tumor response in the table below.

Tumor response (central review, total patient population, N = 58)

Best overall response*1	Number of subjects (%)
CR	34 (58.6)
PR	16 (27.6)
SD	2 (3.4)
PD	3 (5.2)
Excluded by pathologic diagnosis*2	2 (3.4)
Unevaluable/Not evaluated	1 (1.7)
Number of responders (CR or PR) (response rate [95% CI], %)	50 (86.2 [74.6, 93.9])

*1, Revised Response Criteria for Malignant Lymphoma (*J Clin Oncol*. 2007;25:579-86); *2, Diagnosed as sALCL by pathological examination at the study site, but not as sALCL by central review.

Regarding safety, deaths during the treatment period or within 30 days after the last dose were observed in 6 patients. The causes of these deaths excluding 3 deaths from ALCL were acute kidney injury/acute myocardial infarction, respiratory failure, and sudden death in 1 subject each; a causal relationship to brentuximab vedotin was ruled out for all of the events.

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

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

Among the submitted evaluation data, PMDA concluded that the most important clinical studies for evaluating the efficacy and safety of brentuximab vedotin were (a) Japanese phase I/II study which evaluated the efficacy and safety in patients with relapsed or refractory CD30-positive HL or sALCL (Study TB-BC010088), (b) foreign phase II study which evaluated the efficacy and safety in patients with relapsed or refractory CD30-positive HL (Study SG035-0003), and (c) foreign phase II study which evaluated the efficacy and safety in patients with relapsed or refractory CD30-positive sALCL (Study SG035-0004). Thus, PMDA decided to evaluate the submitted data, focusing on these 3 studies.

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

Based on the following reviews, PMDA concluded that a certain level of efficacy of brentuximab vedotin in patients with relapsed or refractory HL and sALCL has been demonstrated.

4.(iii).B.(2).1) Efficacy endpoint

The applicant explained the clinical significance of improvement in response rate defined as the primary endpoint of the phase II part of Study TB-BC010088 and Studies SG035-0003 and SG035-0004, which were conducted in patients with relapsed or refractory CD30-positive HL and sALCL as follows:

The clinical significance of improvement in response rate in patients with relapsed or refractory CD30-positive HL and sALCL is high because responses achieved in these patients, for whom no standard therapy has been established, are expected to improve associated symptoms such as B symptoms resulting from a decrease in tumor burden, and have been reported to lead to an improved outcome of subsequent therapies including haematopoietic stem cell transplantation (*Br J Haematol*. 2004;124:645-52, *Ann Oncol*. 2008;19:1312-9, *Biol Blood Marrow Transplant*. 2008;14:741-7, *J Clin Oncol*. 2008;6:2264-71).

PMDA accepted the applicant's explanation.

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

The applicant explained the efficacy of brentuximab vedotin in patients with relapsed or refractory CD30-positive HL and sALCL as the following (a) and (b):

(a) Patients with relapsed or refractory CD30-positive HL

As regards the efficacy in the phase II part of Study TB-BC010088, according to the data submitted after the filing of the application (data cutoff date, May 24, 2013), the primary efficacy endpoint of response (CR or PR) determined by central review was achieved in 6 of 9 subjects (response rate [95% CI], 66.7% [29.9, 92.5]), and the median response duration [range] (in months) was unable to be estimated [2.8, 12.3]. The data submitted at the time of the application (data cutoff date, September 24, 2012) included 2 subjects with CR, 4 subjects with PR and 3 subjects with SD, while the data submitted after the application (data cutoff date, May 24, 2013) included 5 subjects with CR, 1 subject with PR, and 3 subjects with SD.

In Study SG035-0003, the primary efficacy endpoint of response determined by central review was achieved in 76 of 102 subjects (74.5% [64.9, 82.6]), with the median response duration [95% CI] being 6.7 months [3.6, 14.8].

(b) Patients with relapsed or refractory CD30-positive sALCL

As regards the efficacy in the phase II part of Study TB-BC010088, according to the data submitted after the filing of the application (data cutoff date, May 24, 2013), the primary efficacy endpoint of response (CR or PR) determined by central review was achieved in 5 of 5 subjects (100% [54.9, 100]), with the median response duration [95% CI] being 9.7 months [3.1, 9.7]. The data submitted at the time of the application (data cutoff date, September 24, 2012) included 2 subjects with CR, 2 subjects with PR, and 1 subject who had not yet undergone an imaging evaluation, while the data submitted after the application (data cutoff date, May 24, 2013) included 4 subjects with CR and 1 subject with PR.

In Study SG035-0004, the primary efficacy endpoint of response to brentuximab vedotin determined by central review was achieved in 50 of 58 subjects (86.2% [74.6, 93.9]), with the median response duration [95% CI] being 13.2 months [5.7, unable to be estimated].

PMDA considers as follows:

Given the responses to brentuximab vedotin achieved in patients with relapsed or refractory CD30-positive HL and sALCL, a certain level of efficacy in these patients has been demonstrated.

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

As a result of the reviews to be hereinbelow described, PMDA considers that adverse events requiring attention during treatment with brentuximab vedotin include infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy, tumour lysis syndrome, Stevens-Johnson syndrome (SJS), lung disorder, and pancreatitis acute. In spite of that, PMDA concluded that brentuximab vedotin is tolerable if appropriate measures such as monitoring and control of adverse events are taken by physicians with sufficient knowledge and experience of chemotherapy for haematopoietic malignancies. However, due to the very limited clinical experience with brentuximab vedotin in Japanese patients, further safety information should be collected in Japan after the market launch.

The applicant explained that it is necessary to provide a caution about pancreatitis acute after the market launch in Japan, given that the serious cases of pancreatitis acute including deaths have been reported in overseas post-marketing spontaneous reports after the filing of the application [see "4.(iii).B.(3).10) Pancreatitis acute"]. PMDA is currently inquiring with the applicant regarding the need to provide a caution about adverse events other than pancreatitis acute as well, given the relevant information such as overseas post-marketing spontaneous reports.

In addition, results of safety assessment of Study TB-BC010088 were submitted based on data obtained after the filing of the application (up to May 24, 2013). Regarding differences in safety data of the above study, adverse events whose incidence changed by ≥10% between the original data cut off on September 24, 2012 and those cut off on May 24, 2013 were listed in the table below.

PMDA concluded that the inclusion of the safety data submitted after the filing of the application would not change the review results. Thus, the review results given below are described based on the data submitted at the time of the application.

Adverse events reported in Study TB-BC010088 (the diffence of incidence ≥10%)

System organ class Preferred term (MedDRA ver14.1)	Number of subjects (%)							
	Data cutoff date, September 24, 2012				Data cutoff date, May 24, 2013[*1]			
	HL (N = 14)		sALCL (N = 6)		HL (N = 14)		sALCL (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	14 (100)	9 (64)	5 (83)	2 (33)	14 (100)	10 (71)	6 (100)	3 (50)
Blood and lymphatic system disorders								
Neutropenia	6 (43)	2 (14)	5 (83)	0	7 (50)	2 (14)	6 (100)	1 (17)
Leukopenia	9 (64)	2 (14)	3 (50)	0	9 (64)	2 (14)	4 (67)	0
Eosinophilia	2 (14)	0	0	0	2 (14)	0	1 (17)	0
Gastrointestinal disorders								
Diarrhoea	2 (14)	0	1 (17)	0	3 (21)	0	2 (33)	0
Stomatitis	1 (7)	0	1 (17)	0	1 (7)	0	2 (33)	0
General disorders and administration site conditions								
Fatigue	4 (29)	0	1 (17)	0	4 (29)	0	2 (33)	0
Pyrexia	0	0	2 (33)	0	0	0	1 (17)[*2]	0
Influenza like illness	3 (21)	0	0	0	5 (36)	0	1 (17)	0
Immune system disorders								
Hypersensitivity	0	0	0	0	0	0	1 (17)	1 (17)
Infections and infestations								
Upper respiratory tract infection	3 (21)	0	0	0	3 (21)	0	1 (17)	0
Nasopharyngitis	3 (21)	0	1 (17)	0	4 (29)	0	3 (50)	0
Investigations								
Weight decreased	0	0	0	0	2 (14)	0	0	0
Gamma-glutamyltransferase increased	0	0	0	0	0	0	1 (17)	0
Musculoskeletal and connective tissue disorders								
Groin pain	0	0	0	0	0	0	1 (17)	0
Nervous system disorders								
Peripheral sensory neuropathy	8 (57)	0	1 (17)	0	10 (71)	0	2 (33)	0
Headache	3 (21)	0	0	0	2 (14)[*2]	0	1 (17)	0
Skin and subcutaneous tissue disorders								
Pruritus	2 (14)	0	0	0	2 (14)	0	1 (17)	0
Nail disorder	0	0	0	0	0	0	1 (17)	0
Ingrowing nail	0	0	0	0	0	0	1 (17)	0

*1, One subject died due to progressive disease ≥29 days after the last dose. *2, The investigator reconsidered these events as pre-existing symptoms instead of adverse events.

4.(iii).B.(3).1) Differences in safety of brentuximab vedotin between HL and sALCL patients and between Japanese and foreign subjects

The outlines of safety in Studies SG035-0003, SG035-0004, and TB-BC010088 were summarized in the table below.

Summary of safety

	Number of subjects (%)			
	Study SG035-0003 HL (N = 102)	Study SG035-0004 sALCL (N = 58)	Study TB-BC010088	
			HL (N = 14)	sALCL (N = 6)
All adverse events	100 (98)	58 (100)	14 (100)	5 (83)
Adverse events leading to death	0	6 (10)	0	0
Serious adverse events other than deaths	25 (25)	24 (41)	3 (21)	1 (17)
Adverse events of Grade ≥3	56 (55)	36 (52)	9 (64)	2 (33)
Adverse events related to brentuximab vedotin	94 (92)	53 (91)	14 (100)	5 (83)
Adverse events leading to treatment discontinuation	20 (20)	16 (28)	0	0
Adverse events leading to dose reduction	11 (11)	7 (12)	0	0
Adverse events leading to dose delay	48 (47)	23 (40)	5 (36)	0

In addition, all-grade adverse events with 20% difference and Grade ≥3 adverse events with ≥10% difference in incidence between Japanese and foreign patients with either HL or sALCL were listed in the table below.

Adverse events with the incidences different by ≥20% (all Grades) or by ≥10% (Grade ≥3) between Japanese and foreign patients with HL or sALCL (Studies SG035-0003, SG035-0004, TB-BC010088)

System organ class Preferred term	Number of subjects (%)							
	Study SG035-0003*1 HL (N = 102)		Study SG035-0004*1 sALCL (N = 58)		Study TB-BC010088*2 HL (N = 14)		Study TB-BC010088*2 sALCL (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	100 (98)	56 (55)	58 (100)	36 (62)	14 (100)	9 (64)	5 (83)	2 (33)
Blood and lymphatic system disorders								
Neutropenia	22 (22)	20 (20)	12 (21)	12 (21)	6 (43)	2 (14)	5 (83)	0
Anaemia	9 (9)	6 (6)	6 (10)	4 (7)	5 (36)	1 (7)	2 (33)	0
Thrombocytopenia	8 (8)	8 (8)	8 (14)	8 (14)	2 (14)	0	0	0
Leukopenia	1 (<1)	0	1 (2)	1 (2)	9 (64)	2 (14)	3 (50)	0
Lymphopenia	0	0	0	0	12 (86)	8 (57)	4 (67)	2 (33)
Gastrointestinal disorders								
Nausea	43 (42)	0	23 (40)	1 (2)	4 (29)	1 (7)	0	0
Diarrhoea	37 (36)	1 (<1)	17 (29)	2 (3)	2 (14)	0	1 (17)	0
Constipation	16 (16)	0	13 (22)	1 (2)	3 (21)	0	0	0
General disorders and administration site conditions								
Fatigue	47 (46)	2 (2)	22 (38)	3 (5)	4 (29)	0	1 (17)	0
Pyrexia	30 (29)	2 (2)	20 (34)	1 (2)	0	0	2 (33)	0
Infections and infestations								
Cellulitis	1 (<1)	0	2 (3)	1 (2)	0	0	1 (17)	1 (17)
Investigations								
ALT increased	2 (2)	1 (<1)	1 (2)	1 (2)	4 (29)	0	1 (17)	0
AST increased	1 (<1)	0	0	0	3 (21)	0	1 (17)	0
Blood lactate dehydrogenase increased	0	0	0	0	3 (21)	0	2 (33)	0
Metabolism and nutrition disorders								
Hypophosphataemia	0	0	2 (3)	1 (2)	2 (14)	2 (14)	0	0
Nervous system disorders								
Peripheral sensory neuropathy	48 (47)	9 (9)	24 (41)	7 (12)	8 (57)	0	1 (17)	0
Respiratory, thoracic and mediastinal disorders								
Cough	21 (21)	0	10 (17)	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Rash	14 (14)	0	14 (24)	0	5 (36)	0	1 (17)	0

*1, MedDRA ver.13.0; *2, MedDRA ver.14.1

The applicant explained the differences in safety profiles between HL patients and sALCL patients as follows:
Comparing incidences of adverse events in Studies SG035-0003 and SG035-0004 between HL and sALCL, deaths and serious adverse events occurred more frequently in sALCL patients than in HL patients, and some adverse events showed difference in incidences between the 2 patient groups (the events of which the incidences differ by ≥10% were: upper respiratory tract infection, arthralgia, rash, and oedema peripheral). However, there were no clinically significant differences, and safety profiles were considered to be almost similar across these patient groups. Also in Study TB-BC010088, no clear differences were observed in the safety profiles between these patient groups, although there are limitations to such a comparison considering the limited number of subjects.

In addition, the applicant explained the safety of brentuximab vedotin in Japanese patients as follows:
All-grade adverse events of which the incidence was higher by ≥20% in Japanese patients than in foreign patients were lymphopenia, anaemia, neutropenia, leukopenia, ALT increased, AST increased, blood lactate dehydrogenase increased, and rash. Grade ≥3 adverse events of which the incidence was higher by ≥10% in Japanese patients than in foreign patients were lymphopenia, leukopenia, cellulitis, and hypophosphataemia.

Among the above events, as for adverse events related to laboratory values, the difference in incidence between Japanese and foreign subjects was partly attributed to the difference in laboratory schedules between Study TB-BC010088 (using more frequent laboratory testing) and Studies SG035-0003 and SG035-0004. In addition, a causal relationship to brentuximab vedotin was ruled out for the Grade 3 cellulitis reported in Study TB-BC010088 and the event resolved with treatment including antimicrobials without dose delay or dose reduction of brentuximab vedotin. Based on the above, the applicant considered that no clinically relevant problems have been observed in the safety in Japanese patients considering ethnic differences.

PMDA considers as follows:
Since no clear differences have been observed in the safety profiles between HL and sALCL patients based on the results from Studies SG035-0003, SG035-0004, and TB-BC010088, PMDA decided to review the safety of brentuximab vedotin also using the pooled data from the 2 patient populations.

Given that the number of Japanese HL and sALCL patients treated with brentuximab vedotin is very limited and that there are limitations to safety evaluation of brentuximab vedotin in Japanese patients, further safety information in Japanese patients should be collected after the market launch. It is necessary to appropriately provide the information that adverse events whose incidence differed between Japanese and foreign patients especially at Grade ≥3, such as lymphopenia and leukopenia, may occur with a higher incidence in Japanese patients than in foreign patients, using information materials.

4.(iii).B.(3).2) Infusion reaction
The applicant explained the brentuximab vedotin-related infusion reaction as follows:
The results of pooled analysis of the foreign phase II studies (Studies SG035-0003 and SG035-0004) showed that 17 of 160 subjects (11%) experienced infusion reaction.[*1] All events in the 17 subjects were Grade 1 or 2 and not serious, and a causal relationship to brentuximab vedotin could not be ruled out for any of these events. Of the 17 subjects, 15 (88%) experienced infusion reaction before or during Cycle 2. Symptoms associated with infusion reaction reported by ≥3 subjects

were chills (6 subjects), nausea (5 subjects), dyspnoea (4 subjects), pruritus (4 subjects), and cough (3 subjects). No infusion reactions[*1] were reported in Study TB-BC010088.

In the foreign phase I studies, infusion reactions[*2] were reported by 2 of 45 subjects (4%) in Study SG035-0001, 6 of 44 subjects (14%) in Study SG035-0002, 11 of 52 subjects (21%) in Study SGN35-007, and 7 of 56 subjects (13%) in Study SGN35-008A. Among infusion reactions reported in the foreign phase I studies, events in 5 subjects were Grade 3 and included serious anaphylaxis, serious anaphylaxis/hypoxia, infusion related reaction, serious dyspnoea, and pruritus/urticaria (1 subject each). A causal relationship to brentuximab vedotin could not be ruled out for any of these events. Among these, 1 subject who experienced serious anaphylaxis discontinued treatment with brentuximab vedotin due to this event.

*1, Defined as an adverse event considered infusion related reaction by the investigators.
*2, Defined as an adverse event considered a hypersensitivity reaction or an acute infusion related reaction by the investigator in Studies SG035-0001 and SG035-0002, while defined as an adverse event considered an infusion related reaction by the investigator or an adverse event leading to interruption of intravenous infusion of brentuximab vedotin in Studies SGN35-007 and SGN35-008A.

PMDA asked the applicant to explain the premedication for infusion reactions.

The applicant responded as follows:
In Studies SG035-0003, SG035-0004, and TB-BC010088, premedication for infusion reactions was not mandatory, but patients who had experienced an infusion reaction at the previous cycle were allowed to be premedicated in subsequent treatment cycles.

Of 160 patients in Studies SG035-0003 and SG035-0004, 20 subjects received premedication for infusion reactions; 10 subjects received preventive premedication before experiencing an infusion reaction and the other 10 subjects received premedication at the time of dosing of brentuximab vedotin after experiencing an infusion reaction. None of the 10 subjects who received preventive premedication before experiencing an infusion reaction experienced an infusion reaction. Of the remaining 150 subjects who did not receive preventive premedication for infusion reactions, 17 experienced an infusion reaction. These infusion reactions were all Grade 1 or 2, and first occurred during Cycle 1 in 9 subjects, Cycle 2 in 6 subjects, Cycle 3 in 1 subject, and Cycle 15 in 1 subject. To 10 of the 17 subjects who experienced an infusion reaction, premedication was administered at the subsequent doses of brentuximab vedotin and 8 of 10 subjects did not reexperience any further infusion reaction whereas 2 of 10 subjects reexperienced an infusion reaction in spite of receiving premedication. By contrast, to the remaining 7 of the 17 subjects, brentuximab vedotin was administered without premedication even after the occurrence of an infusion reaction, but no recurrences of infusion reaction were observed. No infusion reactions were reported in Study TB-BC010088.

In summary, in Studies SG035-0003 and SG035-0004, infusion reactions occurred in patients who did not receive premedication for infusion reactions but the severity was all Grade 1 or 2, and administration of brentuximab vedotin could be completed or continued with interventions such as temporary stop of infusion after occurrence of infusion reactions. The applicant considered that recommendations for preventive premedication for infusion reactions are not necessary. However, patients who experienced an infusion reaction should be premedicated with drugs such as acetaminophen, antihistamines, and corticosteroids at the time of the subsequent doses of brentuximab vedotin.

PMDA asked the applicant to explain the relationship between the infusion rate of brentuximab vedotin and the incidence of infusion reaction.

The applicant responded as follows:
In Studies SG035-0003 and SG035-0004, brentuximab vedotin was to be administered over 30 minutes, but data regarding infusion rates including those before and after temporary infusion stop were not collected; therefore, the relationship between the infusion rate and the incidence of infusion reaction is unknown. In Study TB-BC010088, where no infusion reactions were reported, brentuximab vedotin was to be administered over approximately 2 hours in the phase I part and, if infusion reaction did not occur, the duration of infusion could be shortened to 30 minutes from Cycle 3, and brentuximab vedotin was to be administered over ≥30 minutes in the phase II part. Based on the above, although the impact of the infusion rate of brentuximab vedotin on the occurrence of infusion reaction is unknown, brentuximab vedotin-related infusion reactions were considered to be controlled by using infusion duration of ≥30 minutes.

Given the general recommendations to reduce infusion rate of monoclonal antibody products at re-administration after occurrence of an infusion reaction (*J Support Oncol*. 2007;5:451-7), careful infusion at a reduced rate is needed also at resuming with brentuximab vedotin after occurrence of an infusion reaction.

PMDA considers as follows:
In the foreign phase I studies, Grade 3 infusion reaction was reported by 5 subjects, but 4 of the 5 patients could continue treatment with brentuximab vedotin. According to the results of pooled analysis of the foreign phase II studies, infusion reactions after administration of brentuximab vedotin generally occurred before or during Cycle 2 and were all Grade ≤2, and these infusion reactions improved with interventions such as temporary infusion stop or the use of antihistamines etc. Based on these results, infusion reactions after administration of brentuximab vedotin are considered manageable with appropriate interventions on occurrence. Taking account of the premedication practices and incidence of infusion reaction in clinical studies, there is less need to recommend premedication at the time of the initial dose of brentuximab vedotin, and the need for premedication in patients who have experienced an infusion reaction is unclear. In addition, information on the infusion rate of brentuximab vedotin has not been collected in clinical studies, and the impact of the infusion rate of brentuximab vedotin on the incidence of infusion reaction is also unknown.

Based on the above, the information on the incidence of infusion reaction and interventions upon occurrence in clinical studies should be appropriately disseminated. In addition, a precautionary statement should be included in the package insert, etc. to ensure appropriate interventions upon occurrence of an infusion reaction.

4.(iii).B.(3).3) Neuropathy peripheral
The applicant explained the brentuximab vedotin-related neuropathy peripheral as follows:
The incidence of neuropathy peripheral in Studies SG035-0003, SG035-0004, and TB-BC010088 was as shown in the table below.

Neuropathy peripheral* (Studies SG035-0003, SG035-0004, and TB-BC010088)

Preferred term	Number of subjects (%)			
	Pooled data from Studies SG035-0003 and SG035-0004 (N = 160)		Study TB-BC010088 (N = 20)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Peripheral sensory neuropathy	72 (45)	16 (10)	9 (45)	0
Peripheral motor neuropathy	15 (9)	3 (2)	0	0
Paraesthesia	9 (6)	0	0	0
Demyelinating polyneuropathy	3 (2)	3 (2)	0	0
Neuralgia	3 (2)	1 (<1)	0	0
Hypoaesthesia	2 (1)	0	0	0
Muscular weakness	2 (1)	1 (<1)	0	0
Burning sensation	1 (<1)	0	0	0
Gait disturbance	1 (<1)	0	0	0
Nerve conduction studies abnormal	1 (<1)	0	0	0
Polyneuropathy	1 (<1)	1 (<1)	0	0

* Adverse events based on Standardised MedDRA queries (MedDRA ver.13.0 for Studies SG035-0003 and SG035-0004, MedDRA ver.14.1 for Study TB-BC010088)

In the pooled analysis of Studies SG035-0003 and SG035-0004, neuropathy peripheral was reported by 89 of 160 subjects (56%); Grade 3 neuropathy peripheral was reported by 21 of 160 subjects (13%), and no Grade ≥4 event was reported. Brentuximab vedotin-related neuropathy peripheral resulted in treatment discontinuation of brentuximab vedotin in 19 of 160 subjects (12%) (peripheral sensory neuropathy in 12 subjects, peripheral motor neuropathy in 3 subjects, demyelinating polyneuropathy in 2 subjects, muscular weakness in 1 subject, neuralgia in 1 subject), dose reduction in 14 of 160 subjects (9%), dose delay in 24 of 160 subjects (15%), and temporary infusion stop in 1 of 160 subjects (1%). The incidence of the first occurrence of neuropathy peripheral in these studies was 25% (40 of 160 subjects), 34% (33 of 98 subjects), 28% (10 of 36 subjects), and 50% (6 of 12 subjects) during Cycles 1 to 4, 5 to 8, 9 to 12, and 13 to 16, respectively; the incidences increased with increasing treatment cycles. Likewise, the incidence of the first occurrence of Grade 3 neuropathy peripheral was 1% (2 of 160 subjects), 2% (2 of 126 subjects), 12% (9 of 78 subjects), and 18% (8 of 45 subjects), respectively, showing higher incidences during the later cycles.

Neuropathy peripheral was generally reversible, with the median duration from its occurrence to resolution or improvement being 16 weeks. Out of 89 patients who experienced neuropathy peripheral of any grade, 15 patients (17%) were unresolved (i.e., other than resolved or improved), and out of 21 patients who experienced Grade 3 neuropathy peripheral, 3 patients (14%) were unresolved at the last observation after the end of administration of brentuximab vedotin (at approximately 1 year after the safety follow-up visit). The severity of neuropathy peripheral in the latter 3 patients remained as Grade 3 at the last observation.

In Study TB-BC010088, neuropathy peripheral was reported by 9 of 20 subjects (45%), including Grade 2 events in 1 of 20 subjects (5%) and Grade 1 events in 8 of 20 subjects (40%). A causal relationship of neuropathy peripheral to brentuximab vedotin could not be ruled out for any of the events. Brentuximab vedotin-related neuropathy peripheral did not result in treatment discontinuation, dose reduction, or dose delay of brentuximab vedotin in any patient.

A number of patients already had neuropathy peripheral at the start of treatment with brentuximab vedotin due to the effect of prior therapies for the target disease; 39 of 160 subjects (24%) had concurrent neuropathy peripheral at the start of treatment with brentuximab vedotin in the pooled analysis of Studies SG035-0003 and SG035-0004 (32 subjects had Grade 1 and 7 subjects had Grade 2 neuropathy peripheral). However, the applicant considered that there were no clear differences in the incidence and severity of neuropathy peripheral after administration of

brentuximab vedotin depending on the complication.

PMDA considers as follows:
Although brentuximab vedotin-related neuropathy peripheral was generally reversible, since more than 1 patient remained unresolved (including those with Grade 3 neuropathy peripheral) at the last observation, precautions are necessary to ensure that appropriate actions are available. Thus, information on the rough standards, specified in the clinical studies, of dose delay and dose reduction of brentuximab vedotin should be provided via the package insert, etc. [see "4.(iii).B.(6).3) Criteria for dose delay, dose reduction, and discontinuation"].

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

The applicant explained the brentuximab vedotin-related bone marrow depression as follows:
Adverse events of bone marrow depression that occurred with an incidence of ≥10% in the pooled analysis of Studies SG035-0003 and SG035-0004 or in Study TB-BC010088 are shown in the table below.

Bone marrow depression* (incidence ≥10%) (Studies SG035-0003, SG035-0004, and TB-BC010088)

Preferred term	Number of subjects (%)			
	Pooled analysis of Studies SG035-0003 and SG035-0004 (N = 160)		Study TB-BC010088 (N = 20)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia	34 (21)	32 (20)	11 (55)	2 (10)
Anaemia	15 (9)	10 (6)	7 (35)	1 (5)
Thrombocytopenia	16 (10)	16 (10)	2 (10)	0
Leukopenia	2 (1)	1 (<1)	12 (60)	2 (10)
Lymphopenia	0	0	16 (80)	10 (50)

Bone marrow depression determined as an adverse event by the investigator; *, Adverse events classified into the system organ class "blood and lymphatic system disorders" (MedDRA ver.13.0 for the pooled analysis, MedDRA ver.14.1 for Study TB-BC010088) (excluding lymphadenopathy and eosinophilia, which were not considered as a bone marrow depression).

In the pooled analysis of Studies SG035-0003 and SG035-0004, neutropenia leading to dose reduction and dose delay of brentuximab vedotin was reported by 1 of 160 subjects (1%) and 23 of 160 subjects (14%), respectively, and thrombocytopenia leading to dose reduction and dose delay was reported by 2 of 160 subjects (1%) and 7 of 160 subjects (4%), respectively. In addition, related bleeding events (Grade 3 haematemesis) were reported by 1 of 5 subjects who experienced Grade 4 thrombocytopenia, and a causal relationship to brentuximab vedotin could not be ruled out for any of these events. There was no patient who discontinued the administration of brentuximab vedotin due to neutropenia and thrombocytopenia.

In Study TB-BC010088, neutropenia resulted in dose delay of brentuximab vedotin in 1 of 20 subjects (5%), but did not result in treatment discontinuation or dose reduction in any patient. Thrombocytopenia did not result in treatment discontinuation, dose reduction, or dose delay in any patient.

No events of febrile neutropenia were reported in Studies SG035-0003, SG035-0004, or TB-BC010088, but Grade 4 and 3 febrile neutropenia were reported by 1 patient each in foreign phase I studies of SGN35-007 and SGN35-008A.

In the pooled analysis aforesaid and in Study TB-BC010088, Grade ≥3 laboratory abnormalities related to bone marrow depression included neutrophil count decreased (19 of 158 subjects [12%] and 2 of 20 subjects [10%], respectively), haemoglobin decreased (7 of 158 subjects [4%] and 1 of 20 subjects [5%], respectively), platelet count decreased (10 of 156 subjects [6%] and 0

subjects, respectively), white blood cell count decreased (9 of 158 subjects [6%] and 2 of 20 subjects [10%], respectively), and lymphocyte count decreased (30 of 158 subjects [19%] and 8 of 20 subjects [40%], respectively).

PMDA considers as follows:
Since bone marrow depression reported in Studies SG035-0003, SG035-0004, and TB-BC010088 were largely resolved with dose delay alone, brentuximab vedotin-related bone marrow depression can be controlled with appropriate interventions such as dose delay. Therefore, information on the rough standards, specified in the clinical studies, of dose delay and dose reduction of brentuximab vedotin should be provided via the package insert, etc. in order to ensure appropriate intervention upon occurrence of bone marrow depression [see "4.(iii).B.(6).3) Criteria for dose delay, dose reduction, and discontinuation"].

4.(iii).B.(3).5) Infection
The applicant explained the brentuximab vedotin-related infection as follows:
In the pooled data from Studies SG035-0003 and SG035-0004, infection was reported by 98 of 160 subjects (61%). Grade 3 or 4 infection was reported by 14 of 160 subjects (9%), but no Grade 5 infection was reported. Brentuximab vedotin was delayed in 18 of 160 subjects (11%), but there was no patient who discontinued the administration. Adverse events reported by ≥5% of patients were upper respiratory tract infection (49 of 160 subjects [31%]), sinusitis (13 of 160 subjects [8%]), bronchitis (12 of 160 subjects [8%]), urinary tract infection (9 of 160 subjects [6%]), and herpes zoster (8 of 160 subjects [5%]). Serious adverse events were reported by 16 of 160 subjects (10%) and a causal relationship to brentuximab vedotin could not be ruled out for pneumocystis jiroveci pneumonia (PCP), pneumonia, staphylococcal bacteraemia, urinary tract infection, and neutropenia/pneumonia/urinary tract infection in 1 subject each. The relationship between neutropenia or lymphopenia and infection was investigated by checking for the presence of infection within 7 days after the onset of neutropenia or lymphopenia. No apparent chronological relationship was found between the times of onset of neutropenia or lymphopenia and infection in most cases.

In Study TB-BC010088, infection was reported by 10 of 20 subjects (50%). Grade 3 infection was reported by 2 of 20 subjects (10%), but no Grade ≥4 events were reported. Among these, serious adverse events were cellulitis, meningitis aseptic, PCP, and pneumonia in 1 subject each, and a causal relationship to brentuximab vedotin could not be ruled out for the events in 3 subjects excluding the cellulitis. All these events resolved or improved with dose delay of brentuximab vedotin or drug therapy. As in the foreign phase II studies, no apparent chronological relationship was observed between the times of onset of neutropenia or lymphopenia and infection.

In foreign phase I studies, 2 deaths from infection for which a causal relationship to brentuximab vedotin could not be ruled out were reported; 1 subject (who received 3.6 mg/kg of brentuximab vedotin in Study SG035-0001) developed febrile neutropenia/septic shock, and the other (who participated in Study SGN35-008A) haemorrhage intracranial/cytomegalovirus infection/pancytopenia.

PMDA asked the applicant to explain the prophylaxis practices against infections in Studies SG035-0003, SG035-0004, and TB-BC010088.

The applicant responded as follows:
In Studies SG035-0003, SG035-0004, and TB-BC010088, prophylaxis against infections was not prespecified.

In Studies SG035-0003 and SG035-0004, 43 of 160 subjects received antiviral medication in order to prevent herpes virus infection, and 2 of the 43 subjects (5%) experienced herpes virus

infection (herpes simplex and herpes virus infection in 1 subject each). Of the remaining 117 subjects who did not receive antiviral medication, 10 (9%) experienced herpes virus infection (herpes zoster in 7 subjects, herpes simplex in 3 subjects, oral herpes in 1 subject). Out of a total of 160 subjects, 32 subjects received medication such as trimethoprim/sulfamethoxazole in order to prevent PCP and none of the 32 subjects experienced PCP. Of the remaining 128 subjects who did not receive medication such as trimethoprim/sulfamethoxazole, 1 subject (1%) experienced PCP.

In Study TB-BC010088, where no antiviral medication was used, 2 of 20 subjects (10%) experienced herpes virus infection (herpes simplex and oral herpes in 1 subject each). Seven subjects received medication such as trimethoprim/sulfamethoxazole and none of them experienced PCP. Of the remaining 13 subjects who did not receive medication such as trimethoprim/sulfamethoxazole, 1 subject (8%) experienced PCP.

Given the facts that severe infections associated with brentuximab vedotin have been observed and that patients with HL or sALCL are immunocompromised due to their immunodeficiency, PMDA asked the applicant to explain (a) the need to provide a caution for patients with a history of infections, etc., (b) the effect of brentuximab vedotin on decreased immune function and its recovery, and (c) the clinical consequences resulting from binding of brentuximab vedotin to activated lymphocytes expressing CD30.

The applicant responded as follows:
Regarding the point (a), Grade 3 bronchopulmonary aspergillosis was reported by a patient with a history of oral candidiasis in Study SG035-0003, but a causal relationship to brentuximab vedotin was ruled out. In addition, 1 patient in Studies SG035-0004 and 2 patients in TB-BC010088 had a history or presence of infections (1 patient with a history of herpes simplex/herpes zoster, 1 patient with a history of PCP, 1 patient with concurrent candidiasis); among these, 1 patient each experienced Grade 1 oral herpes and Grade 2 herpes simplex after administration of brentuximab vedotin and the other 1 patient did not experience infection after administration of brentuximab vedotin. Based on the above, although infections after administration of brentuximab vedotin can be controlled with appropriate interventions, appropriate cautions should be provided for patients with a history or presence of infections because potential safety risks due to relapse of diseases such as herpes zoster cannot be ruled out.

Regarding the point (b), although factors involved in humoral or cellular immunity (e.g., immunoglobulins) were not determined in the clinical studies of brentuximab vedotin, taking into account that 9 of 15 subjects (60%) who experienced Grade ≥3 lymphopenia in the pooled data from the foreign phase II studies (Studies SG035-0003 and SG035-0004) and that 2 of 8 subjects (25%) who experienced Grade ≥3 lymphopenia in Study TB-BC010088 did not recover to baseline lymphocyte count at 30 days after the last dose of brentuximab vedotin, recovery from the decreased immune function due to brentuximab vedotin may take a long time. However, relapsed or refractory HL or sALCL patients are immunocompromised due to their immunodeficiency caused by the primary disease or prior therapies, and periodic evaluation of immune function including lymphocyte count is expected as part of disease management also during treatment with brentuximab vedotin in these patients; therefore, immune function after administration of brentuximab vedotin can be appropriately managed.

Regarding the point (c), CD30 has reported to be expressed on activated lymphocytes and involved in proliferation and activation etc. of lymphocytes (*Clin Chim Acta*. 2012;413:1338-49). Although timing of expression and functions of CD30 in lymphocytes remains unclear, based on the reports that productions of IL-5 and IFN-γ are induced along with CD30 expression in T cells (*Ann N Y Acad Sci*. 2002;975:101-13, *Biol Chem*. 2012;393:101-6), CD30 may be involved in immune response during a particular period. Thus, the possibility that the immune function may

be affected by the binding of brentuximab vedotin to activated lymphocytes expressing CD30 cannot be ruled out, but its clinical consequences remain unknown.

PMDA considers as follows:
Brentuximab vedotin-related infections did not result in treatment discontinuation in any patient and resolved during the study period after dose delay of brentuximab vedotin in all the cases in Studies SG035-0003, SG035-0004, and TB-BC010088. Adverse events of infection can be managed by appropriate actions including interventions against infections and dose delay of brentuximab vedotin. However, since serious events including death in a foreign phase I study have been observed, information on the incidence of infections in clinical studies should be appropriately provided via the package insert, etc.

In addition, the impact of medications such as antiviral drugs on the prevention of infections remains unknown, and therefore, it is necessary to collect information on the implementation and details of prophylaxis including antiviral medication as well as the incidence of infections in routine clinical settings. Furthermore, given the possibility that the binding of brentuximab vedotin to CD30-positive normal T cells might affect immune function and result in easily infectible condition as well as the fact that the relationship between alterations in immune factors after administration of brentuximab vedotin and incidence of infections is unclear, it is necessary to continue to collect information including literature sources and appropriately provide information if a new finding becomes available.

4.(iii).B.(3).6) Progressive multifocal leukoencephalopathy (PML)
The applicant explained the brentuximab vedotin-related progressive multifocal leukoencephalopathy (PML) as follows:
No events of PML were reported in Studies SG035-0003, SG035-0004, or TB-BC010088. Serious PML was reported by 1 subject in Study SGN35-010* and the patient resulted in death due to PML. This event was assessed as PML for which a causal relationship to brentuximab vedotin could not be ruled out based on MRI findings and JC virus detection in cerebrospinal fluid etc. In addition, PML and suspected PML were reported by 1 subject each according to overseas post-marketing spontaneous reports (data cutoff date, August 18, 2012). The patient with PML showed a trend towards recovery, but the patient with suspected PML, with no definitive MRI findings, was reported to have died due to bulbar disorder, acute progressive ascending paralysis associated with mental status changes, and HL after haematopoietic stem-cell transplantation. The symptoms of PML occurred after administration of brentuximab vedotin in Cycle 3, 2, or 8, respectively.

* The extension study of foreign phase III study (SGN35-005, a placebo-controlled comparative study in patients with CD30-positive HL at high risk for relapse due to residual disease after ASCT), in which brentuximab vedotin was administered in patients who had received placebo and experienced HL progressed in Study SGN35-005.

PMDA considers as follows:
PML is a progressive and fatal disease which develops on the background of decreased cellular immunity due to underlining medical conditions including human immunodeficiency virus infection, haematopoietic malignancies, autoimmune disease, organ transplantation, and treatment with antineoplastic drugs or immunosuppressants (Clinical Practice Guideline for Progressive Multifocal Leukoencephalopathy 2013 [Research Group on Prion Disease and Delayed Viral Infection, Research on Overcoming Intractable Disease supported by the Health and Labour Sciences Research Grants, 2013]), and therefore caution should be exercised for the occurrence of PML during treatment for HL or sALCL patients irrespective of use of brentuximab vedotin. Since serious PML occurred after administration of brentuximab vedotin, leading to death in some patients, information on the incidence of PML reported to date should be

appropriately provided via the package insert, etc.

4.(iii).B.(3).7) Tumour lysis syndrome (TLS)

The applicant explained the incidence of brentuximab vedotin-related tumour lysis syndrome (TLS) as follows:

TLS was reported by 1 patient each in Study SG035-0004 and in overseas post-marketing spontaneous reports (data cutoff date, August 18, 2012). In 1 patient in Study SG035-0004, Grade 3 TLS for which a causal relationship to brentuximab vedotin could not be ruled out was observed on Day 1 of Cycle 1, and in the other patient, who received treatment for diffuse large B-cell lymphoma as an off-label use, TLS was observed approximately 1 week after the first dose. Both patients recovered with treatment including infusion therapy. No events of TLS were reported in Studies TB-BC010088 or SG035-0003.

PMDA considers as follows:

Given that serious TLS for which a causal relationship to brentuximab vedotin could not be ruled out was observed and that Grade 4 uric acid level increased was reported by 2 of 58 subjects (4%) including the subject with serious TLS after administration of brentuximab vedotin in Study SG035-0004, it is necessary to pay attention to occurrence of TLS after the start of brentuximab vedotin therapy, and appropriate precautionary statements should be included in the package insert etc. about the incidence of TLS reported to date.

4.(iii).B.(3).8) Stevens-Johnson syndrome (SJS)

The applicant explained the incidence of brentuximab vedotin-related SJS as follows:

SJS was reported by 1 patient each in Study SG035-0003 and in overseas post-marketing spontaneous reports (data cutoff date, August 18, 2012). The treatment with brentuximab vedotin was discontinued due to SJS in both patients, and they recovered with interventions including steroid treatment. The SJS in Study SG035-0003 occurred after administration of brentuximab vedotin in Cycle 2 and the other SJS occurred after administration in Cycle 7. No events of SJS were reported in Studies TB-BC010088 or SG035-0004.

PMDA considers as follows:

Given the facts that SJS for which a causal relationship to brentuximab vedotin could not be ruled out was observed, leading to treatment discontinuation of brentuximab vedotin, and that SJS may progress in severity if it develops, it is necessary to carefully monitor for the incidence of SJS after administration of brentuximab vedotin and to take appropriate actions if any abnormalities are found. Thus, the package insert should appropriately include precautionary statements about the incidence of SJS reported to date.

4.(iii).B.(3).9) Lung disorders

The applicant explained the incidence of lung disorders after administration of brentuximab vedotin alone as follows:

Hypoxia was reported by 1 of 44 subjects (2%) in Study SG035-0002; the event was assessed as serious but a causal relationship to brentuximab vedotin was ruled out. Pulmonary toxicity was reported by 7 of 102 subjects (7%) in Study SG035-0003, including pneumonitis (3 subjects), lung disorder (2 subjects), and hypoxia, pulmonary fibrosis, and radiation pneumonitis (1 subject each). Among these, events in 2 subjects were assessed as serious adverse events, and a causal relationship to brentuximab vedotin could not be ruled out for pneumonitis (1 subject). The event of pneumonitis occurred after administration of brentuximab vedotin in Cycle 3 and the treatment with brentuximab vedotin was discontinued. Pulmonary toxicity was reported by 6 of 52 subjects (12%) in Study SGN35-007, including hypoxia (4 subjects), lung infiltration (2 subjects), and radiation pneumonitis, respiratory distress, and respiratory failure (1 subject each). Among these, hypoxia (2 subjects) and radiation pneumonitis, respiratory distress, and respiratory failure (1 subject each) were assessed as serious adverse events, and a causal relationship to brentuximab

vedotin could not be ruled out for hypoxia (2 subjects). Hypoxia in 2 subjects (1 serious event, 1 non-serious event) was reported as infusion reactions. Events leading to death were not reported in the above studies. Pulmonary toxicity was reported by 2 of 58 subjects (3%) in Study SG035-0004, including pulmonary oedema and respiratory failure (1 subject each). Both of the events were assessed as serious adverse events, and respiratory failure in 1 subject resulted in death. A causal relationship to brentuximab vedotin was ruled out for both events. No events of pulmonary toxicity were reported in Studies SG035-0001, SGN35-008A, or TB-BC010088.

Regarding the incidence of pulmonary toxicity after concomitant use of brentuximab vedotin with other antineoplastic drugs, as described in "4.(iii).B.(6).4) Concomitant use with other antineoplastic drugs," the incidence of lung disorders after concomitant use of brentuximab vedotin with bleomycin hydrochloride (bleomycin) was higher than that after administration of brentuximab vedotin alone. The applicant explained that, based on the above, concomitant use of brentuximab vedotin with bleomycin will be contraindicated.

PMDA asked the applicant to explain the incidence of lung disorders after administration of brentuximab vedotin reported from foreign post-marketing experience.

The applicant responded as follows:
As lung disorders for which a causal relationship to brentuximab vedotin could not be ruled out, respiratory failure (5 subjects), pneumonitis (4 subjects), lung infiltration (3 subjects), interstitial lung disease, lung disorder, and pulmonary alveolar haemorrhage (2 subjects each), and acute respiratory distress syndrome, acute respiratory failure, organising pneumonia, pulmonary toxicity, radiation pneumonitis, and respiratory distress (1 subject each) have been reported in foreign post-marketing experience (data cutoff date, [redacted], 20[redacted]). All events excluding lung infiltration (1 subject) were assessed as serious adverse events. Respiratory failure (3 subjects) and pneumonitis, pulmonary alveolar haemorrhage, and respiratory distress (1 subject each) resulted in death.

PMDA considers as follows:
Given that serious events including pneumonitis for which a causal relationship to brentuximab vedotin could not be ruled out occurred, appropriate precautionary statements should be included in the package insert etc. In addition, information on the previous incidence of lung disorders after administration of brentuximab vedotin, including that from foreign post-marketing experience, should be appropriately disseminated. PMDA accepted the applicant's explanation that concomitant use of brentuximab vedotin with bleomycin will be contraindicated [see "4.(iii).B.(6).4) Concomitant use with other antineoplastic drugs"].

4.(iii).B.(3).10) Pancreatitis acute

The applicant explained the incidence of brentuximab vedotin-related pancreatitis acute as follows:
As of June 27, 2013 after the application, serious pancreatitis acute was reported by 12 subjects after administration of brentuximab vedotin, including those from overseas post-marketing spontaneous reports. Pancreatitis acute reported by 6 of the 12 subjects was assessed as the events for which a causal relationship to brentuximab vedotin could not be ruled out, and of these, 1 subject resulted in death due to the event. Out of the 6 subjects, 5 subjects experienced pancreatitis acute after administration of brentuximab vedotin in Cycle 1 or 2, and the other 1 subject experienced pancreatitis acute after the third dose of brentuximab vedotin (given once weekly). In addition, a relapse of pancreatitis acute was reported by 1 of 4 subjects who received readministration of brentuximab vedotin after recovery from pancreatitis acute. No events of pancreatitis acute were reported in Studies SG035-0003, SG035-0004, or TB-BC010088.

PMDA considers as follows:

Since serious pancreatitis acute including a fatal event occurred after administration of brentuximab vedotin, attention should be paid to occurrence of pancreatitis acute by means of, for example, periodic examination including pancreatic enzyme test, and appropriate precautionary statements should be included in the package insert etc. about the incidence of pancreatitis acute reported to date.

4.(iii).B.(3).11) Others

(a) Hepatic function disorder

The applicant explained the incidence of brentuximab vedotin-related hepatic function disorder as follows:

ALT increased (2 subjects), and hepatic steatosis, hepatic mass, transaminase increased, biopsy liver, and AST increased (1 subject each) were reported in Study SG035-0003, and among these, Grade ≥3 events were ALT increased, transaminase increased, and hepatic steatosis (1 subject each) (Grade 3 in all events). Transaminase increased (2 subjects), and ALT increased and liver function test abnormal (1 subject each) were reported in Study SG035-0004, and among these, Grade ≥3 events were transaminase increased (Grade 3) and ALT increased (Grade 4) (1 subject each). ALT increased (5 subjects) and AST increased (4 subjects) were reported in Study TB-BC010088, but no Grade ≥3 events were reported.

In addition to the above adverse events that were assessed as adverse events by the investigator, the incidence of liver function tests worsened by ≥1 grade after the start of brentuximab vedotin is shown in the table below.

Incidence of liver function tests worsened by ≥1 grade
(Studies SG035-0003 and SG035-0004 [pooled analysis], Study TB-BC010088)

Preferred term	Number of subjects (%)							
	Pooled data from Studies SG035-0003 and SG035-0004 (N = 160[*1])				Study TB-BC010088 (N = 20)			
	Worsened by 1 grade	Worsened by 2 grades	Worsened by 3 grades	Worsened by 4 grades	Worsened by 1 grade	Worsened by 2 grades	Worsened by 3 grades	Worsened by 4 grades
ALT increased	50 (31)	3 (2)	1[*2] (1)	0	8 (40)	1 (5)	0	0
Albumin decreased	15[*2] (9)	1 (1)	0	0	3 (15)	0	0	0
Alkaline phosphatase increased	28 (18)	2 (1)	0	0	4 (20)	0	0	0
AST increased	58 (36)	5[*2] (3)	0	0	8 (40)	0	0	0
Bilirubin increased	2 (1)	2 (1)	0	0	0	0	0	0

*1, Baseline values were obtained in 156 subjects for ALT increased and AST increased, in 158 subjects for albumin decreased, in 157 subjects for alkaline phosphatase increased, and 147 subjects for bilirubin increased.; *2, Grade 3 liver function test abnormal was reported by 1 subject each with ALT increased and with albumin decreased in Study SG035-0003, and by 1 subject with AST increased in Study SG035-0004.

PMDA considers as follows:

Although a few subjects developed hepatic function disorder as adverse events in Studies SG035-0003, SG035-0004, and TB-BC010088, given the facts that about half of subjects showed a worsening trend in AST and ALT and that hepatotoxicity (necrotizing hepatitis lesions, thickening and hyperplasia of the bile duct associated with epithelial necrosis and pericholangitis) was observed in rat repeated-dose toxicity study [see "3.(iii).A.(6).2) Mechanistic studies of toxicity"], it is necessary to provide an appropriate caution about the risks of hepatic function disorder after administration of brentuximab vedotin based on the currently available study data.

(b) Hyperglycaemia

The applicant explained the incidence of brentuximab vedotin-related hyperglycaemia as follows:
In the pooled analysis of Studies SG035-0003 and SG035-0004, hyperglycaemia or blood glucose increased as an adverse event was reported by 9 of 160 subjects (6%). Among these, Grade 3 hyperglycaemia was reported by 5 subjects, and a causal relationship to brentuximab vedotin could not be ruled out for the events in 4 of these 5 subjects. No Grade 4 events were reported. Blood glucose increased of Grade ≥3 as a laboratory abnormality was reported by 9 of 160 subjects (6%). Exclusion criteria did not include patients with prior or concurrent diabetes mellitus or hyperglycaemia in these studies.

In Study TB-BC010088, hyperglycaemia or blood glucose increased as an adverse event or Grade ≥3 blood glucose increased as a laboratory abnormality was not reported. Diabetes mellitus patients with hemoglobin A_{1c} of ≥7.0% at screening were excluded from this study.

Findings suggesting hyperglycaemia or histopathological changes in the pancreas were not found in the non-clinical studies and the mechanism of hyperglycaemia or diabetes mellitus associated with brentuximab vedotin remains unknown.

PMDA asked the applicant to explain the incidence of hyperglycaemia or diabetes mellitus according to the presence or absence of prior or concurrent diabetes mellitus.

The applicant responded as follows:
Out of a total of 160 subjects in Studies SG035-0003 and SG035-0004, 21 subjects had concurrent hyperglycaemia or diabetes mellitus before the start of brentuximab vedotin, and among these, 6 subjects (29%) experienced a worsening of disease after administration of brentuximab vedotin. In addition, of the remiaining 139 subjects who did not have prior or concurrent diabetes mellitus or hyperglycaemia, 6 subjects (4%) experienced hyperglycaemia after administration of brentuximab vedotin. Thus, although hyperglycaemia may occur after administration of brentuximab vedotin irrespective of the presence or absence of prior or concurrent diabetes mellitus, no cases of hyperglycaemia or diabetes mellitus leading to treatment discontinuation of brentuximab vedotin were reported and administration of brentuximab vedotin could be continued under glycemic control with medical therapies etc. in Studies SG035-0003 and SG035-0004.

PMDA considers as follows:
Given that Grade 3 hyperglycaemia for which a causal relationship to brentuximab vedotin could not be ruled out occurred and that some patients required glycemic control by treatment with insulin or hypoglycemic agent etc., attention should be paid to the occurrence of hyperglycaemia and caution should be exercised appropriately for the incidence.

(c) Anti-therapeutic antibody (ATA)

The applicant explained the ATA as follows:
Out of 160 subjects enrolled in Studies SG035-0003 and SG035-0004, 157 subjects (98%) had both baseline and post-dose measurements. Of the 157 subjects, 8 subjects were determined as ATA-positive at baseline and excluded from the analysis. Of the remaining 149 subjects, 96 (64%) were determined as negative, 42 (28%) as transient positive (i.e., positive at 1 or 2 testing points), and 11 (7%) as persistent positive (i.e., positive at ≥3 testing points) after the administration of brentuximab vedotin. The median treatment duration was 25 weeks in negative subjects (range, 3.0-75.0 weeks), transient positive subjects (range, 5.0-54.0 weeks), and 43 weeks in persistent positive subjects (range, 15.0-51.0 weeks), indicating a tendency for treatment duration in persistent positive subjects to be similar to or longer than that in negative or transient positive subjects. Adverse events were reported by 136 of 138 subjects (99%) in the negative and transient positive groups and 11 of 11 patients (100%) in the persistent positive group, and Grade

≥3 adverse events were reported by 79 of 138 subjects (57%) and 5 of 11 subjects (45%), respectively; thus, no tendency was observed for the incidence of adverse events to clearly differ between negative and transient positive subjects and persistent positive subjects. However, infusion reaction was reported by 7 of 96 negative subjects (7%), 5 of 42 transient positive subjects (12%), and 3 of 11 persistent positive subjects (27%), with the incidence being higher in persistent positive subjects.

In Study TB-BC010088, 17 of 20 subjects had both baseline and post-dose measurements. Of the 17 subjects, 3 subjects were determined as ATA-positive at baseline. Of the remaining 14 subjects, 8 subjects (57%) were determined as negative, 5 subjects (36%) were determined as transient positive, and 1 subject (7%) was determined as persistent positive.

PMDA considers as follows:
At present, the safety of brentuximab vedotin in patients with ATA is not clear. Therefore, it is necessary to provide information appropriately if a new finding about the relationship between ATA and the safety of brentuximab vedotin becomes available in the ongoing clinical studies etc.

4.(iii).B.(4) Clinical positioning
PMDA confirmed the descriptions of brentuximab vedotin for treatment of relapsed or refractory HL and sALCL in world-renowned textbooks on clinical oncology and overseas clinical practice guidelines, which were as described in (a) and (b) below:

(a) Relapsed or refractory HL
- NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (v.2.2013): Treatment with brentuximab vedotin alone is an option for the treatment of relapsed or refractory HL.

- Williams Hematology, 8th edition (McGraw-Hill Companies, Inc. 2010, USA): Responses were achieved with brentuximab vedotin in 2 phase I studies in patients with refractory HL (Studies SG035-0001 and SG035-0002).

There was no description of brentuximab vedotin in the National Cancer Institute Physician Data Query (NCI-PDQ) (dated August 30, 2012).

(b) Relapsed or refractory sALCL
- NCCN Non-Hodgkin's Lymphoma Clinical Practice Guidelines in Oncology (v.1.2013) (NCCN guidelines): Treatment with brentuximab vedotin alone is an option for the treatment of patients with relapsed or refractory sALCL regardless of whether haematopoietic stem cell transplantation is indicated for the patients or not.

PMDA asked the applicant to explain the clinical positioning of brentuximab vedotin in the treatment of relapsed or refractory HL and sALCL.

The applicant responded as follows:
(a) Relapsed or refractory HL
Clinical practice guidelines do not exist in Japan, and therefore, overseas clinical practice guidelines etc. are used as references for clinical treatment. Combination chemotherapy is the standard for the initial therapy for HL, and approximately 20% to 30% of patients who received a combination regimen with doxorubicin, bleomycin, vinblastine sulfate (vinblastine), and dacarbazine (ABVD regimen) have been reported to experience relapsed or refractory disease after the treatment (*Int J Hematol*. 2010;92:713-24, *Jpn J Clin Oncol*. 2000;30:146-52). Patients with relapsed or refractory HL after the initial therapy who experienced relapsed or refractory disease after autologous stem cell transplant (ASCT) or for whom ASCT is not indicated have been subjected to treatment such as rescue therapy using the above combination chemotherapy

etc. but do not have any standard therapies available. Brentuximab vedotin will be a treatment option for patients with relapsed or refractory CD30-positive HL because a certain level of efficacy and manageable safety profile were demonstrated in Study SG035-0003 in patients with relapsed or refractory CD30-positive HL who had a history of combination chemotherapy and ASCT and in Study TB-BC010088 in patients with relapsed or refractory CD30-positive HL who had a history of combination chemotherapy.

(b) Relapsed or refractory sALCL

Clinical practice guidelines do not exist in Japan, and therefore, overseas clinical practice guidelines etc. have been used as references for clinical treatment. A combination regimen with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen) or similar combination regimens have been commonly used as the initial therapy for ALCL, but 40% to 65% of patients have been reported to experience a recurrence in spite of good responses to the initial therapy (*Blood.* 2008;111:5496-504). Patients with sALCL who experienced relapsed or refractory disease have been subjected to treatment such as combination chemotherapies and ASCT, but do not have any standard therapies available. Brentuximab vedotin is a treatment option for patients with relapsed or refractory CD30-positive sALCL because a certain level of efficacy and manageable safety profile were demonstrated in Studies SG035-0004 and TB-BC010088 in patients with relapsed or refractory CD30-positive sALCL who had a history of combination chemotherapy.

A foreign phase III study (Study C25003) in patients with previously untreated CD30-positive HL and a global phase III study (Study SGN35-014) in patients with previously untreated CD30-positive mature T-cell lymphoma including sALCL are ongoing and the primary endpoint analyses are planned to be performed in or around 20[redacted].

PMDA considers as follows:

Based on the reviews described in this section and sections "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," PMDA concluded that brentuximab vedotin may be positioned as a treatment option for patients with relapsed or refractory CD30-positive HL and sALCL.

4.(iii).B.(5) Indication

The proposed indication of brentuximab vedotin was "Following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma." In addition, the applicant explained at the time of the application that the following precautionary statements will be included in the Precautions for Indications section: (a) eligible patients should be selected with full knowledge of the information in the "Clinical Studies" section and sufficient understanding of the efficacy and safety of brentuximab vedotin and (b) the disease to be indicated for brentuximab vedotin should be diagnosed by a physician or a medical institution well experienced in pathologic diagnosis.

Based on the results of reviews described in this section below and sections "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Clinical positioning," PMDA concluded that the proposed indication "Following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma" is appropriate and that the following precautionary statements should be included in the Precautions for Indications section of the package insert.

- Eligible patients should be selected 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 patients who are confirmed to be positive for CD30 antigen with the immunohistological or other appropriate methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

4.(iii).B.(5).1) Use in patients with primary cutaneous ALCL limited to the skin

Studies SG035-0004 and TB-BC010088 were conducted in patients with relapsed or refractory sALCL and there is no clinical experience of brentuximab vedotin in patients with primary cutaneous ALCL (pcALCL), but the applicant explained the use of brentuximab vedotin in pcALCL patients as follows:

In Study TB-BC010088, pcALCL patients who had widespread visceral involvement similar to that seen in sALCL patients were permitted to enroll, and 6 subjects were enrolled as pcALCL patients with visceral involvement. Skin lesions were completely resolved during the study in 3 of the 6 subjects. Grade 3 cellulitis occurred in 1 of the 3 subjects, but the treatment could be continued with interventions. In Study SG035-0004, 15 of 58 subjects (26%) had malignant skin lesions at baseline, and 14 of the 15 subjects showed complete clearance of skin lesions. In addition, there is a report on a foreign phase II open-label study of brentuximab vedotin in patients with CD30-positive primary cutaneous lymphoma including pcALCL that all of the 3 enrolled pcALCL patients achieved a response (*Blood.* 2012;120:3688).

In addition to the above findings, Japanese clinical practice guidelines have recommended treatment with antineoplastic drug alone as the first-line treatments for pcALCL patients with widespread lesions who have difficulty with radiotherapy, while recommending radiotherapy as the first-line treatment for pcALCL (Clinical practice guidelines for malignant skin tumor II: Cutaneous Lymphoma [*Jpn J Dermatol.* 2009;119:1189-211]). Therefore, brentuximab vedotin is considered as a treatment option for patients with relapsed or refractory pcALCL, for which treatment with antineoplastic drug alone is indicated.

A foreign phase III study (Study C25001) is ongoing in patients with CD30-positive mycosis fungoides and pcALCL, and is expected to report the results in the latter half of 20[redacted].

PMDA considers as follows:

Given the fact, for example, that the NCCN guidelines recommend brentuximab vedotin as a treatment option for sALCL other than pcALCL, there is no evidence for actively recommending treatment with brentuximab vedotin in pcALCL patients. However, for the following reasons, there is little need to specifically describe the term “systemic” in the Indications section, given that the populations evaluated in the clinical studies are stated in the Precautions for Indications section.

- In Studies SG035-0004 and TB-BC010088, enrollment of pcALCL patients who had widespread visceral involvement similar to that seen in sALCL patients was permitted, and data from Study TB-BC010088 showed no difference in the efficacy and safety of brentuximab vedotin between patients who were enrolled as pcALCL patients with visceral involvement and patients with sALCL.

- Taking into account that brentuximab vedotin is to be used by physicians with adequate knowledge and experience in chemotherapy for haematopoietic malignancies, appropriate patient selection would be ensured by correctly informing the target patient populations evaluated in the clinical studies.

4.(iii).B.(5).2) Use in patients with relapsed or refractory HL without a prior history of ASCT

Study SG035-0003 was conducted in patients with relapsed or refractory HL after ASCT, and therefore, brentuximab vedotin was not used in patients with relapsed or refractory HL without a history of ASCT in this study. However, the applicant explained the use of brentuximab vedotin in patients with relapsed or refractory HL without a history of ASCT as follows:

Among clinical studies of brentuximab vedotin in HL patients, foreign phase I studies (Studies SG035-0001 and SG035-0002) and Study TB-BC010088 were planned to enroll patients who were judged ineligible for ASCT by the investigator or patients who refused treatment with ASCT in addition to patients with relapsed or refractory HL after ASCT. The number of responders (response rate [95% CI]) in Studies SG035-0001 and SG035-0002 by history of ASCT was 6 of 20 patients without a history of ASCT (30% [11.9, 54.3]) and 29 of 60 patients with a history of ASCT (48% [35.2, 61.6]). The number of responders (response rate [95% CI]) in Study TB-BC010088 by history of ASCT was 5 of 6 patients without a history of ASCT (83% [35.9, 99.6]) and 4 of 8 patients with a history of ASCT (50% [15.7, 84.3]). In addition, the applicant considered that no clear differences exist in the safety profile of brentuximab vedotin between HL patients with and without a history of ASCT in the above 3 studies, although there are limitations in such a comparison due to the limited number of patients.

PMDA considers as follows:
No clinical studies have been conducted that compare the efficacy of brentuximab vedotin and ASCT in patients with relapsed or refractory HL, and the clinical usefulness of brentuximab vedotin in patients with relapsed or refractory HL without a history of ASCT is unknown. However, given the fact that responders were observed among patients with relapsed or refractory HL without a history of ASCT in Studies SG035-0001, SG035-0002, and TB-BC010088, there is little need to specify the history of ASCT in the Indications section, given that the populations evaluated in the clinical studies are stated in the Precautions for Indications section.

4.(iii).B.(5).3) Expression study for CD30

The methods for assaying CD30 expression (immunohistochemical [IHC] and flow cytometric [FCM] assays) and definition of CD30-positivity used in Studies SG035-0003, SG035-0004, and TB-BC010088 were as shown in the table below.

Assay methods for CD30 expression and definitions of CD30-positivity

	Study SG035-0003	Study SG035-0004	Study TB-BC010088
Assay method	IHC assay	IHC assay	IHC assay or FCM assay
Definition of positivity	Cell membrane or cytoplasm of Reed-Sternberg cells or Reed-Sternberg-like cells is determined to be CD30-positive by the above method at the central laboratory.	Cell membrane of the hallmark cells (medium sized cells containing a kidney bean-shaped nucleus and a paranuclear eosinophilic region, so-called doughnut cells) is determined to be CD30-positive by the above method at the central laboratory.	Tumor cells are documented to be CD30-positive in the report by the trial site based on IHC or FCM assay.

PMDA asked the applicant to explain (a) eligibility for administering brentuximab vedotin to subjects with inconsistent assay results between IHC and FCM methods in Study TB-BC010088 and (b) eligibility for administering brentuximab vedotin to CD30-negative patients.

The applicant responded as follows:
Regarding the point (a), 3 of 20 subjects in Study TB-BC010088 were subjected to the expression test for CD30 by both the IHC and FCM assays, and all the 3 subjects were determined to be positive by both assays; thus, both methods showed consistency in positivity/negativity. The remaining 17 subjects underwent the expression test by the IHC assay only. Even in the case inconsistent results between IHC and FCM assays are obtained, diagnosis of CD30-positivity in HL or sALCL patients is performed based on comprehensive evaluation of the morphological observations using an IHC assay and hematoxylin-eosin (HE) staining and the results of an FCM assay etc., and patients who have been determined to have CD30-positive HL or sALCL are considered as candidates for treatment with brentuximab vedotin.

Regarding the point (b), all clinical studies of brentuximab vedotin were conducted in CD30-positive patients, and no clinical experience in patients with CD30-negative HL or sALCL has been reported even after the market launch outside Japan. In Study SG035-0004, which was conducted in sALCL patients, 1 subject was determined as CD30-positive at the trial site and enrolled in the study but was not determined as CD30-positive by central review. This patient received 1.8 mg/kg of brentuximab vedotin but discontinued brentuximab vedotin after administration in Cycle 3 due to the patient's refusal to continue treatment. The best response determined by central review was CR, and the reported Grade ≥3 adverse events included peripheral motor neuropathy and peripheral sensory neuropathy.

PMDA considers as follows:
Brentuximab vedotin is an antibody-drug-conjugate targeting CD30 and has been developed for treatment of CD30-positive patients who are expected to respond from a pharmacological point of view. Thus, a precautionary statement should be included in the Precautions for Indications section to ensure that CD30-positivity is confirmed appropriately.

4.(iii).B.(6) Dosage and administration
Based on the following reviews, PMDA concluded that the proposed dosage and administration "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" is acceptable. In addition, the following precautionary statements should be included in the Precautions for Dosage and Administration section.

- The efficacy and safety of the combination therapy of brentuximab vedotin with other antineoplastic drugs have not been established.

- Preparation of injectable solution and infusion duration: Reconstitute the contents of one vial with 10.5 mL of Water for Injection (JP), and dilute a suitable volume with Isotonic Sodium Chloride Solution (JP) or 5% Glucose Injection (JP) to make a 0.4 to 1.2 mg/mL solution. The diluted solution should be intravenously infused over at least 30 minutes.

- If an adverse drug reaction occurred after administration of brentuximab vedotin, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Criteria for dose delay, dose reduction, and discontinuation in patients with neuropathy peripheral

NCI-CTCAE 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 neuropathy improves to Grade ≤1 or baseline. If the patient has recovered, 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.

Criteria for dose delay, dose reduction, and discontinuation in patients with neutropenia

NCI-CTCAE Grade *	Measures
Grade 1 (<LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)	Continue dosing at the same dose regimen.
Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)	Hold dosing until neutropenia improves to Grade ≤2 or baseline. If the patient has recovered, resume treatment at the same dose regimen.

LLN, Lower limit of normal; *, Based on NCI-CTCAE v3.0

4.(iii).B.(6).1) Dose and dosing interval

The applicant explained the dose and dosing interval of brentuximab vedotin as follows:

The MTD of brentuximab vedotin was determined to be 1.8 mg/kg in Study SG035-0001, in which brentuximab vedotin was to be administered every 3 weeks at doses of 0.1 to 3.6 mg/kg. In addition, the safety data from Study SG035-0002, in which brentuximab vedotin was to be administered on Days 1, 8, and 15 in each cycle of 28 days, were compared to the data from Studies SG035-0001, SG035-0003, and SG035-0004. As a result, the incidence and severity of neuropathy peripheral tended to be higher in Study SG035-0002 adopting a more frequent dosing schedule, therefore, every 3-week dosing was selected as the dosing interval of brentuximab vedotin.

The efficacy and manageable safety profile were demonstrated in Studies SG035-0003 and SG035-0004, in both of which brentuximab vedotin was to be administered every 3 weeks at a dose of 1.8 mg/kg [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"]. In these studies, 94 of 160 subjects (59%) received dose modification (dose delay, dose reduction, or discontinuation), and the dose modifications in 79 of 160 subjects (49%) were due to adverse events. Major adverse events leading to dose modification of brentuximab vedotin included neutropenia (23 of 160 subjects [13%]) and peripheral sensory neuropathy (25 of 160 subjects [16%]).

In Study TB-BC010088, in which brentuximab vedotin was to be administered every 3 weeks at a dose of 1.8 mg/kg, similar efficacy and safety results were found when compared to Studies SG035-0003 and SG035-0004 [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"]. Adverse events leading to dose reduction or discontinuation of brentuximab vedotin were not reported in any patient, but dose delay of brentuximab vedotin due to adverse events including leukopenia and neutropenia was reported by 5 of 17 subjects in the 1.8 mg/kg cohort. No apparent ethnic differences in the pharmacokinetics of brentuximab vedotin have been observed in the results of this study or foreign clinical studies (Studies SG035-0001 and SGN35-008A) [see "4.(ii).B.(1) Difference in the PK of brentuximab vedotin between Japanese and foreign subjects"].

Based on the above, the dose and dosing interval used in studies SG035-0003, SG035-0004, and TB-BC010088, that is, 1.8 mg/kg of brentuximab vedotin once every 3 weeks, were proposed as dose regimen of brentuximab vedotin for the treatment of relapsed or refractory CD30-positive HL or sALCL.

PMDA accepted the applicant's explanation.

4.(iii).B.(6).2) Number of doses

The applicant explained the number of doses of brentuximab vedotin as follows:

In Study SG035-0001, tumor response was to be determined after Cycle 2, and patients who were determined to have achieved CR, PR, SD, or clinical benefit were to receive an additional 2 cycles of treatment. Whether to continue treatment after Cycle 4 was to be discussed between the investigator and the sponsor (Seattle Genetics, Inc.), and the maximum number of doses was not prespecified. Among 42 HL patients and 2 sALCL patients enrolled in Study SG035-0001, 1 HL

patient continued to receive treatment of 16 cycles which was longest in the study; this patient discontinued treatment with brentuximab vedotin due to PD.

Based on the results from Study SG035-0001, the upper limit of the number of treatment cycles was defined as 16 cycles in Studies SG035-0003 and SG035-0004. In Study SG035-0003, the median number of treatment cycles was 9, and 18 of 102 subjects (18%) received 16 cycles of treatment. In Study SG035-0004, the median number of treatment cycles was 7, and 10 of 58 subjects (17%) received 16 cycles of treatment. In Japanese phase I/II study (Study TB-BC010088), the upper limit of the number of treatment cycles of brentuximab vedotin was defined as 16 cycles as is the case with Studies SG035-0003 and SG035-0004. The median number of treatment cycles was 8, and 2 of 20 subjects (10%) received 16 cycles of treatment.

PMDA asked the applicant to explain the need to state the maximum number of doses of brentuximab vedotin in the Dosage and Administration section of the package insert.

The applicant responded as follows:
A foreign phase II study (Study SGN35-006) has been conducted since [redacted] 20[redacted] to evaluate the safety and efficacy of extended treatment with and re-administration* of brentuximab vedotin, in which 13 HL patients and 6 sALCL patients (14 subjects receiving extended treatment, 5 subjects receiving re-administration) have received brentuximab vedotin for >16 cycles (data cutoff date, [redacted] [redacted], 20[redacted]). Because the upper limit of the number of treatment cycles of brentuximab vedotin was defined as 16 cycles in Study TB-BC010088, there has been no clinical experience of >16 cycles of treatment with brentuximab vedotin in Japanese patients.

* "Extended treatment" was defined as treatment continuation with brentuximab vedotin in patients who had completed 16 cycles of study treatment without intolerable toxicity in a previous clinical study of brentuximab vedotin. "Re-administration" was defined as re-treatment with brentuximab vedotin in patients who had achieved CR or PR in a previous clinical study of brentuximab vedotin but then experienced disease progression or relapse.

Among adverse events with an incidence of ≥25% of the 19 subjects who received brentuximab vedotin beyond Cycle 16 throughout the treatment period in Study SGN35-006, those whose incidence of the first occurrence were similar between Cycles 1 to 16 and from Cycle 17* included peripheral sensory neuropathy (10 of 19 subjects [53%] and 4 of 9 subjects [44%], respectively), upper respiratory tract infection (8 of 19 subjects [42%] and 4 of 11 subjects [36%], respectively), headache (4 of 19 subjects [21%] and 3 of 15 subjects [20%], respectively), and sinusitis (3 of 19 subjects [16%] and 3 of 16 subjects [19%], respectively). Other adverse events including fatigue, muscle spasms, alopecia, arthralgia, cough, neutropenia, pyrexia, diarrhoea, and rash tended to occur mainly by Cycle 16.

* The incidence among patients who had not experienced the adverse event up to Cycle 16.

Grade ≥3 adverse events that occurred in or after Cycle 17 were reported by 7 of 19 subjects (37%) and included neutropenia (3 subjects), peripheral sensory neuropathy (2 subjects), and deep vein thrombosis, dehydration, and peripheral motor neuropathy (1 subject each). Grade ≥4 adverse events were not reported. A serious adverse event of Grade 3 thrombocytopenia was reported by 1 subject. Adverse events leading to treatment discontinuation of brentuximab vedotin in or after Cycle 17 were reported by 3 of 19 subjects (16%) and included peripheral motor neuropathy (2 subjects) and peripheral sensory neuropathy (1 subject).

The response rate [95% CI] (determined by the investigator) in the above 19 subjects was 95% [74, 99.9] (18 of 19 subjects).

The applicant explained that, based on the above, given that (i) there were no clear differences in the safety profile between Cycles 1 to 16 and from Cycle 17 and the safety profile of brentuximab vedotin was considered to be manageable in or after Cycle 17, and that (ii) the treatment options available are very limited for patients with relapsed or refractory HL and sALCL, target diseases of brentuximab vedotin, there is less need to set the maximum number of doses for the dose regimen of brentuximab vedotin.

PMDA considers as follows:
In Study SG035-0001, the maximum number of treatment cycles was not defined and brentuximab vedotin was eventually administered up to Cycle 16. Based on this, the maximum number of doses was set for the subsequent phase. Thus, there is no clinical pharmacological rationale for selecting 16 cycles as the maximum number of doses. However, given the very limited clinical experience of >16 cycles of treatment with brentuximab vedotin, when information causing safety concerns of long term treatment of brentuximab vedotin is obtained from the ongoing clinical studies etc., prompt communication of the information is needed. In addition, information on the absence of clinical experience of >16 cycles of treatment in Japanese patients should be appropriately disseminated.

4.(iii).B.(6).3) Criteria for dose delay, dose reduction, and discontinuation

The applicant explained the reason for proposing inclusion of a precautionary statement describing the rough standards for dose delay, dose reduction, or discontinuation of brentuximab vedotin upon occurrence of neuropathy peripheral and neutropenia during treatment with brentuximab vedotin in the Precautions for Dosage and Administration section as follows:
Major adverse events leading to dose modification of brentuximab vedotin in Studies SG035-0003 and SG035-0004 were neuropathy peripheral and neutropenia [see "4.(iii).B.(6).1) Dose and dosing interval"], the statement for the Precautions for Dosage and Administration section was proposed by referring to the dose adjustment requirements upon occurrence of these events used in Studies SG035-0003, SG035-0004, and TB-BC010088. There is less need to include the rough standards for dose delay, dose reduction, or discontinuation of brentuximab vedotin upon occurrence of bone marrow depression other than neutropenia in the package insert because such events could largely be managed by dose delay of brentuximab vedotin.

The dose adjustment criteria for neuropathy peripheral and neutropenia were largely similar among Studies SG035-0003, SG035-0004, and TB-BC010088. Details of and reasons for the changes from the requirements of clinical studies to the statements for the package insert are shown below.

(a) Neuropathy peripheral

In Studies SG035-0003, SG035-0004, and TB-BC010088, the statement provided that if Grade 2 neuropathy peripheral occurs, treatment of brentuximab vedotin should be held until recovery from the event, and dosing should be resumed after recovery to Grade ≤1 at the same dose as that prior to the dose modification. In addition, a decision on treatment discontinuation upon occurrence of Grade 3 neuropathy peripheral was to be discussed between the investigator and the sponsor.

In Studies SG035-0003 and SG035-0004, symptoms worsened in 7 of 21 subjects (33%) who continued to receive brentuximab vedotin without dose modification and in 2 of 10 subjects (20%) who continued to receive brentuximab vedotin at a reduced dose after experiencing Grade 2 neuropathy peripheral, while in 22 subjects who had dose delay, symptoms did not worsen during the period of interruption. In addition, of 21 subjects who experienced Grade 3 neuropathy peripheral, 17 discontinued treatment with brentuximab vedotin and the remaining 4 subjects continued to receive treatment without dose modification. Symptoms worsened in 2 of the 4 patients. Based on the above, Grade 2 and 3 neuropathy peripheral were considered manageable

by dose delay and dose reduction of brentuximab vedotin. For this reason, the Precautions for Dosage and Administration section was to state that treatment with brentuximab vedotin should be resumed at a reduced dose of 1.2 mg/kg after recovery from the event.

(b) Neutropenia
In Studies SG035-0003, SG035-0004, and TB-BC010088, the statement provided that if Grade 4 neutropenia for which a causal relationship to brentuximab vedotin could not be ruled out occurs, treatment of brentuximab vedotin should be held until recovery to Grade ≤2, and dosing should be resumed after recovery to Grade ≤2 at the same dose as that prior to the dose modification or at a reduced dose of 1.2 mg/kg, with consideration given to treatment with recombinant human granulocyte colony-stimulating factor (G-CSF).

In Studies SG035-0003 and SG035-0004, Grade 4 neutropenia was reported by 11 subjects and brentuximab vedotin was discontinued due to the event in 2 subjects. The remaining 9 subjects continued treatment with brentuximab vedotin for ≥2 cycles after experiencing neutropenia; 8 subjects had (3-21 days) dose delay of brentuximab vedotin or received G-CSF preparation, and 1 subject had dose reduction of brentuximab vedotin to 1.2 mg/kg. Based on the above, it is considered that brentuximab vedotin can be continued without dose reduction upon occurrence of Grade 4 neutropenia by using dose delay of brentuximab vedotin and treatment with G-CSF preparation. For this reason, the Precautions for Dosage and Administration section was to state that if Grade 4 neutropenia occurs, treatment of brentuximab vedotin should be held until recovery to Grade ≤2 and dosing should be resumed at the same dose regimen after recovery to Grade ≤2 with consideration given to treatment with G-CSF preparation.

PMDA considers as follows:
PMDA accepted the applicant's explanation except for the statement regarding treatment with G-CSF preparation upon occurrence of neutropenia. Regarding consideration on the treatment with G-CSF preparation upon occurrence of neutropenia, as it is a standard symptomatic treatment for neutropenia, there is little need to specifically include the statement in the Precautions for Dosage and Administration section. Instead using relevant materials is considered appropriate to provide information (including experience in clinical studies).

4.(iii).B.(6).4) Concomitant use with other antineoplastic drugs
The applicant explained concomitant use of brentuximab vedotin with other antineoplastic drugs as follows:
The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs are unknown, and therefore brentuximab vedotin is unlikely to be used in combination with other antineoplastic drugs. However, a precautionary statement to the effect that the efficacy and safety of brentuximab vedotin used concomitantly with other antineoplastic drugs have not been established and that concomitant use with other antineoplastic drugs should be avoided will be included in the Precautions for Dosage and Administration section of the package insert.

Ongoing clinical studies of brentuximab vedotin used concomitantly with other antineoplastic drugs include (a) Study SGN35-009 in patients with previously untreated HL (combination study with ABVD or that with doxorubicin + vinblastine + dacarbazine [AVD]), (b) Study SGN35-011 in patients with previously untreated CD30-positive mature T-cell and natural killer cell tumor (combination study with cyclophosphamide + doxorubicin + prednisone [CH-P] or that with CHOP), (c) Study SGN35-014 in patients with previously untreated CD30-positive mature T-cell lymphoma (comparative study between brentuximab vedotin + CH-P group and CHOP group), and (d) Study C25003 in patients with previously untreated CD30-positive classical HL (comparative study between brentuximab vedotin + AVD group and ABVD group).

Among these 4 studies, pulmonary toxicity was reported by 11 of 25 subjects (44%) in the brentuximab vedotin + ABVD group of Study SGN35-009, including pulmonary toxicity in 9 subjects and hypoxia, interstitial lung disease, and pneumonitis in 1 subject each. Among these, Grade ≥3 events were reported by 6 of 25 subjects (24%), resulting in 2 deaths due to pulmonary toxicity. However, pulmonary toxicity was not reported by 26 subjects in the brentuximab vedotin + AVD group. In Study SGN35-011, pulmonary toxicity was reported by 4 of 39 subjects (10%), including respiratory failure in 2 subjects and acute respiratory failure, pneumonitis, and pulmonary oedema in 1 subject each. No events that come under pulmonary toxicity were reported in Studies C25003 or SGN35-014.

As described above, the incidence of pulmonary toxicity was high in patients who received brentuximab vedotin concomitantly with bleomycin in Study SGN35-009; therefore, administration of brentuximab vedotin to patients who are receiving bleomycin will be listed in the Contraindications section of the package insert. The impact of concomitant use of brentuximab vedotin with antineoplastic drugs other than bleomycin on the risk of pulmonary toxicity is unknown.

PMDA considers as follows:
PMDA accepted the applicant's explanation. However, if information on safety issues related to concomitant use of brentuximab vedotin with other antineoplastic drugs is obtained from future clinical study data etc., it is necessary to appropriately provide the information.

4.(iii).B.(7) Post-marketing investigations
The applicant plans to conduct a post-marketing surveillance covering all patients treated with brentuximab vedotin in order to evaluate the safety of brentuximab vedotin under routine use in patients with relapsed or refractory CD30-positive HL or sALCL after the market launch.

The applicant explained the post-marketing surveillance plan as follows:
The following adverse events that were commonly reported in Japanese and foreign clinical studies and that may affect the continuation of treatment with brentuximab vedotin will be investigated as a priority: neuropathy peripheral, infections, neutropenia, and infusion reaction.

In the pooled analysis of the foreign phase II studies (Studies SG035-0003 and SG035-0004), the incidence of neuropathy peripheral, infections, Grade ≥3 neutropenia, and infusion reaction was 56%, 61%, 20%, and 11%, respectively. Referring to the incidence of infusion reaction (11%), the least common adverse event among the items, the sample size was planned to be 140 subjects in order to observe ≥10 subjects for each priority survey item with a 95% probability.

The observation period was planned to be 16 cycles from the start of treatment with brentuximab vedotin for the following reasons:

- In a foreign clinical study (Study SGN35-006) where the safety in or after Cycle 17 was evaluated, major adverse events tended to occur by Cycle 16.

- New safety concerns are not considered to emerge in or after Cycle 17 because the events whose first occurrence was reported in or after Cycle 17 (peripheral sensory neuropathy, upper respiratory tract infection, fatigue, muscle spasms, headache, neutropenia, sinusitis, decreased appetite, peripheral motor neuropathy, dizziness, abdominal pain, erythema) were all observed with similar severity in the 2 foreign phase II studies (Studies SG035-0003 and SG035-0004), which limited the number of treatment cycles to ≤16.

PMDA considers as follows:
The number of patients enrolled in the Japanese phase I/II study (Study TB-BC010088) was limited (n = 20) and it is necessary to promptly collect information in an unbiased way via the post-marketing surveillance and to promptly provide the obtained safety information to healthcare professionals.

The priority investigation items and target sample size proposed by the applicant for the post-marketing surveillance are acceptable. In addition, taking account of the results from Study SGN35-006, no concerns warranting evaluation of long-term safety of brentuximab vedotin were identified, and therefore, the planned observation period of up to 16 cycles is also acceptable.

4.(iii).B.(8) Development of brentuximab vedotin in pediatric patients
PMDA asked the applicant to explain the status of development of dose regimen of brentuximab vedotin for pediatric patients with CD30-positive HL and ALCL.

The applicant responded as follows:
Currently, a phase I/II study (Study C25002) of brentuximab vedotin monotherapy in pediatric patients with relapsed or refractory HL (≥ 5 and < 18 years of age) or ALCL (≥ 2 and < 18 years of age) is ongoing in Europe and the US, and the primary analysis is planned to be performed in [redacted] 20[redacted]. Development in Japanese patients will be considered taking account of the results of this study.

PMDA considers as follows:
In order to develop dose regimen of brentuximab vedotin for Japanese pediatric patients with HL and ALCL without lagging behind foreign countries, the applicant should collect and analyze information on development demand for products for pediatric patients and also obtain information on the development plan of brentuximab vedotin in foreign countries to take appropriate actions such as participation in foreign clinical studies.

4.(iv) Adverse events, etc. observed in clinical studies
Of the clinical data submitted for safety evaluation, deaths are described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than deaths are shown below.

4.(iv).(1) Japanese phase I/II study (Study TB-BC010088)
Adverse events were reported by 3 of 3 subjects (100%) in the 1.2 mg/kg group of the phase I part, 3 of 3 subjects (100%) in the 1.8 mg/kg group of the phase I part, 9 of 9 subjects (100%) in the HL group of the phase II part, and 4 of 5 subjects (80%) in the sALCL group of the phase II part, and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 3 of 3 subjects (100%) in the 1.2 mg/kg group of the phase I part, 3 of 3 subjects (100%) in the 1.8 mg/kg group of the phase I part, 9 of 9 subjects (100%) in the HL group of the phase II part, and 4 of 5 subjects (80%) in the sALCL group of the phase II part. Adverse events with an incidence of ≥20% in any group were as shown in the following table.

Adverse events with an incidence of ≥20% (data cutoff date, September 24, 2012)

System organ class Preferred term (MedDRA ver. 14.1)	Number of subjects (%)							
	Phase I part				Phase II part			
	1.2 mg/kg group		1.8 mg/kg group		HL group		sALCL group	
	N = 3		N = 3		N = 9		N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (67)	3 (100)	1 (33)	9 (100)	6 (67)	4 (80)	2 (40)
Blood and lymphatic system disorders								
Lymphopenia	3 (100)	2 (67)	2 (67)	1 (33)	8 (89)	5 (56)	3 (60)	2 (40)
Leukopenia	2 (67)	0	1 (33)	0	7 (78)	2 (22)	2 (40)	0
Neutropenia	1 (33)	0	0	0	6 (67)	2 (22)	4 (80)	0
Anaemia	2 (67)	1 (33)	1 (33)	0	3 (33)	0	1 (20)	0
Gastrointestinal disorders								
Nausea	1 (33)	1 (33)	1 (33)	0	2 (22)	0	0	0
General disorders and administration site conditions								
Fatigue	1 (33)	0	0	0	3 (33)	0	1 (20)	0
Infections and infestations								
Nasopharyngitis	1 (33)	0	1 (33)	0	2 (22)	0	0	0
Investigations								
ALT increased	0	0	1 (33)	0	3 (33)	0	1 (20)	0
AST increased	0	0	1 (33)	0	2 (22)	0	1 (20)	0
Blood lactate dehydrogenase increased	2 (67)	0	0	0	2 (22)	0	1 (20)	0
Metabolism and nutrition disorders								
Decreased appetite	1 (33)	1 (33)	0	0	3 (33)	0	0	0
Nervous system disorders								
Peripheral sensory neuropathy	2 (67)	0	1 (33)	0	6 (67)	0	0	0
Skin and subcutaneous tissue disorders								
Rash	1 (33)	0	1 (33)	0	3 (33)	0	1 (20)	0

Serious adverse events were reported by 1 of 3 subjects (33%) in the 1.2 mg/kg group of the phase I part, 2 of 9 subjects (22%) in the HL group of the phase II part, and 1 of 5 subjects (20%) in the sALCL group of the phase II part. The reported serious adverse events were meningitis aseptic (1 subject) in the 1.2 mg/kg group of the phase I part, PCP and pneumonia (1 subject each) in the HL group of the phase II part, and cellulitis (1 subject) in the sALCL group of the phase II part. Of these, a causal relationship to brentuximab vedotin could not be ruled out for meningitis aseptic (1 subject) in the 1.2 mg/kg group of the phase I part and PCP and pneumonia (1 subject each) in the HL group of the phase II part.

There were no adverse events leading to treatment discontinuation of brentuximab vedotin.

In addition, safety results of Study TB-BC010088 based on data as of May 24, 2013 were submitted after the filing of the application. Adverse events were reported by 3 of 3 subjects (100%) in the 1.2 mg/kg group of the phase I part, 3 of 3 subjects (100%) in the 1.8 mg/kg group of the phase I part, 9 of 9 subjects (100%) in the HL group of the phase II part, and 5 of 5 subjects (100%) in the sALCL group of the phase II part, and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 3 of 3 subjects (100%) in the 1.2 mg/kg group of the phase I part, 3 of 3 subjects (100%) in the 1.8 mg/kg group of the phase I part, 9 of 9 subjects (100%) in the HL group of the phase II part, and 5 of 5 subjects (100%) in the sALCL group of the phase II part. Adverse events with an incidence of ≥20% in any group were as shown in the following table.

Adverse events with an incidence of ≥20% (data cutoff date, May 24, 2013)

System organ class Preferred term (MedDRA ver. 14.1)	Number of subjects (%)							
	Phase I part				Phase II part			
	1.2 mg/kg group		1.8 mg/kg group		HL group		sALCL group	
	N = 3		N = 3		N = 9		N = 5	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (67)	3 (100)	2 (67)	9 (100)	6 (67)	5 (100)	3 (60)
Blood and lymphatic system disorders								
Lymphopenia	3 (100)	2 (67)	2 (67)	1 (33)	8 (89)	5 (56)	3 (60)	2 (40)
Leukopenia	2 (67)	0	1 (33)	0	7 (78)	2 (22)	3 (60)	0
Neutropenia	1 (33)	0	0	0	7 (78)	2 (22)	5 (100)	1 (20)
Anaemia	2 (67)	1 (33)	1 (33)	0	3 (33)	0	1 (20)	0
Gastrointestinal disorders								
Nausea	1 (33)	1 (33)	2 (67)	0	2 (22)	0	0	0
Diarrhoea	2 (67)	0	0	0	2 (22)	0	1 (20)	0
General disorders and administration site conditions								
Fatigue	1 (33)	0	0	0	3 (33)	0	2 (40)	0
Influenza like illness	1 (33)	0	1 (33)	0	3 (33)	0	1 (20)	0
Infections and infestations								
Nasopharyngitis	1 (33)	0	1 (33)	0	3 (33)	0	2 (40)	0
Upper respiratory tract infection	0	0	1 (33)	0	2 (22)	0	1 (20)	0
Investigations								
ALT increased	0	0	1 (33)	0	3 (33)	0	1 (20)	0
AST increased	0	0	1 (33)	0	3 (33)	0	1 (20)	0
Blood lactate dehydrogenase increased	2 (67)	0	0	0	2 (22)	0	1 (20)	0
Metabolism and nutrition disorders								
Decreased appetite	1 (33)	1 (33)	0	0	3 (33)	0	0	0
Nervous system disorders								
Peripheral sensory neuropathy	2 (67)	0	1 (33)	0	8 (89)	0	1 (20)	0
Skin and subcutaneous tissue disorders								
Rash	1 (33)	0	1 (33)	0	3 (33)	0	1 (20)	0

Serious adverse events were reported by 1 of 3 subjects (33%) in the 1.2 mg/kg group of the phase I part, 2 of 9 subjects (22%) in the HL group of the phase II part, and 2 of 5 subjects (40%) in the sALCL group of the phase II part. The reported serious adverse events were herpes zoster disseminated, meningitis aseptic, and myelodysplastic syndrome (1 subject each) in the 1.2 mg/kg group of the phase I part; PCP and pneumonia (1 subject each) in the HL group of the phase II part; and cellulitis and hypersensitivity (1 subject each) in the sALCL group of the phase II part. Of these, a causal relationship to brentuximab vedotin could not be ruled out for herpes zoster disseminated, meningitis aseptic, and myelodysplastic syndrome (1 subject each) in the 1.2 mg/kg group of the phase I part; PCP and pneumonia (1 subject each) in the HL group of the phase II part; and hypersensitivity (1 subject) in the sALCL group of the phase II part.

An adverse event leading to treatment discontinuation of brentuximab vedotin was reported by 1 of 3 subjects (33%) in the 1.8 mg/kg group of the phase I part. The reported adverse event leading to treatment discontinuation of brentuximab vedotin was peripheral sensory neuropathy (1 subject) and a causal relationship to brentuximab vedotin could not be ruled out.

4.(iv).(2) Foreign phase I study (Study SG035-0001)

Adverse events were reported by 3 of 3 subjects (100%) in the 0.1 mg/kg group, 2 of 4 subjects (50%) in the 0.2 mg/kg group, 3 of 3 subjects (100%) in the 0.4 mg/kg group, 3 of 3 subjects (100%) in the 0.6 mg/kg group, 3 of 3 subjects (100%) in the 0.8 mg/kg group, 4 of 4 subjects (100%) in the 1.2 mg/kg group, 12 of 12 subjects (100%) in the 1.8 mg/kg group, 12 of 12 subjects (100%) in the 2.7 mg/kg group, and 1 of 1 subject (100%) in the 3.6 mg/kg group, and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 2 of 3 subjects (67%) in the 0.1 mg/kg group, 1 of 4 subjects (25%) in the 0.2 mg/kg group, 3

of 3 subjects (100%) in the 0.4 mg/kg group, 3 of 3 subjects (100%) in the 0.6 mg/kg group, 3 of 3 subjects (100%) in the 0.8 mg/kg group, 3 of 4 subjects (75%) in the 1.2 mg/kg group, 12 of 12 subjects (100%) in the 1.8 mg/kg group, 11 of 12 subjects (92%) in the 2.7 mg/kg group, and 1 of 1 subject (100%) in the 3.6 mg/kg group. Adverse events with an incidence of ≥20% in any group were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.8.0)	Number of subjects (%)									
	0.1 mg/kg group		0.2 mg/kg group		0.4 mg/kg group		0.6 mg/kg group		0.8 mg/kg group	
	N = 3		N = 4		N = 3		N = 3		N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (67)	2 (50)	1 (25)	3 (100)	1 (33)	3 (100)	1 (33)	3 (100)	0
Blood and lymphatic system disorders										
Neutropenia	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders										
Diarrhoea	0	0	2 (50)	0	1 (33)	0	2 (67)	0	1 (33)	0
Nausea	0	0	1 (25)	0	1 (33)	0	1 (33)	0	0	0
Vomiting	0	0	2 (50)	0	1 (33)	0	2 (67)	0	0	0
General disorders and administration site conditions										
Fatigue	1 (33)	0	1 (25)	0	0	0	2 (67)	0	1 (33)	0
Pyrexia	2 (67)	0	1 (25)	0	1 (33)	0	1 (33)	0	1 (33)	0
Nervous system disorders										
Neuropathy peripheral	1 (33)	0	0	0	0	0	0	0	0	0
Headache	1 (33)	0	0	0	1 (33)	0	0	0	0	0

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

System organ class Preferred term (MedDRA ver.8.0)	Number of subjects (%)							
	1.2 mg/kg group		1.8 mg/kg group		2.7 mg/kg group		3.6 mg/kg group	
	N = 4		N = 12		N = 12		N = 1	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	2 (50)	12 (100)	5 (42)	12 (100)	6 (50)	1 (100)	1 (100)
Blood and lymphatic system disorders								
Neutropenia	1 (25)	0	4 (33)	1 (8)	5 (42)	2 (17)	0	0
Gastrointestinal disorders								
Diarrhoea	1 (25)	0	1 (8)	0	1 (8)	0	1 (100)	0
Nausea	0	0	4 (33)	0	2 (17)	0	1 (100)	0
Vomiting	0	0	2 (17)	0	1 (8)	0	1 (100)	1 (100)
General disorders and administration site conditions								
Fatigue	1 (25)	0	4 (33)	0	6 (50)	0	0	0
Pyrexia	0	0	3 (25)	0	5 (42)	2 (17)	1 (100)	1 (100)
Nervous system disorders								
Neuropathy peripheral	1 (25)	0	4 (33)	0	4 (33)	0	0	0
Headache	1 (25)	0	3 (25)	0	3 (25)	0	0	0

Serious adverse events were reported by 2 of 3 subjects (67%) in the 0.1 mg/kg group, 1 of 4 subjects (25%) in the 0.2 mg/kg group, 1 of 3 subjects (33%) in the 0.4 mg/kg group, 2 of 3 subjects (67%) in the 0.6 mg/kg group, 3 of 12 subjects (25%) in the 1.8 mg/kg group, 4 of 12 subjects (33%) in the 2.7 mg/kg group, and 1 of 1 subject (100%) in the 3.6 mg/kg group. The reported serious adverse events were disease progression, hypercalcaemia, and lymphoma (1 subject each) in the 0.1 mg/kg group; disease progression, anaemia, cough, dehydration, haematochezia, and pneumonia (1 subject each) in the 0.2 mg/kg group; myocardial ischaemia (1 subject) in the 0.4 mg/kg group; staphylococcal bacteraemia, bursitis infective staphylococcal, and deep vein thrombosis (1 subject each) in the 0.6 mg/kg group; anaphylaxis, aspergillosis, and syncope (1 subject each) in the 1.8 mg/kg group; pyrexia (2 subjects), staphylococcal bacteraemia,

abdominal pain, clostridium difficile colitis, peripheral sensorimotor neuropathy, prostatitis, acute kidney injury, and sepsis (1 subject each) in the 2.7 mg/kg group; and febrile neutropenia and septic shock (1 subject each) in the 3.6 mg/kg group. Of these, a causal relationship to brentuximab vedotin could not be ruled out for hypercalcaemia (1 subject) in the 0.1 mg/kg group; myocardial ischaemia (1 subject) in the 0.4 mg/kg group; anaphylaxis (1 subject) in the 1.8 mg/kg group; peripheral sensorimotor neuropathy and pyrexia (1 subject each) in the 2.7 mg/kg group; and febrile neutropenia and septic shock (1 subject each) in the 3.6 mg/kg group.

Adverse events leading to treatment discontinuation of brentuximab vedotin were reported by 1 of 3 subjects (33%) in the 0.1 mg/kg group, 1 of 4 subjects (25%) in the 0.2 mg/kg group, 1 of 3 subjects (33%) in the 0.4 mg/kg group, 1 of 3 subjects (33%) in the 0.6 mg/kg group, 1 of 4 subjects (25%) in the 1.2 mg/kg group, 5 of 12 subjects (42%) in the 1.8 mg/kg group, 4 of 12 subjects (33%) in the 2.7 mg/kg group, and 1 of 1 subject (100%) in the 3.6 mg/kg group. The reported adverse events leading to treatment discontinuation of brentuximab vedotin were disease progression (1 subject) in the 0.1 mg/kg group; disease progression (1 subject) in the 0.2 mg/kg group; myocardial ischaemia (1 subject) in the 0.4 mg/kg group; disease progression (1 subject) in the 0.6 mg/kg group; peripheral sensory neuropathy (1 subject) in the 1.2 mg/kg group; fatigue, thrombocytopenia, anaphylaxis, aspergillosis, and neuropathy peripheral (1 subject each) in the 1.8 mg/kg group; fatigue, thrombocytopenia, hyperglycaemia, neutropenia, peripheral sensorimotor neuropathy, and acute kidney injury (1 subject each) in the 2.7 mg/kg group; febrile neutropenia and septic shock (1 subject each) in the 3.6 mg/kg group. Of these, a causal relationship to brentuximab vedotin could not be ruled out for myocardial ischaemia (1 subject) in the 0.4 mg/kg group; peripheral sensory neuropathy (1 subject) in the 1.2 mg/kg group; fatigue, thrombocytopenia, anaphylaxis, and neuropathy peripheral (1 subject each) in the 1.8 mg/kg group; fatigue, thrombocytopenia, hyperglycaemia, neutropenia, and peripheral sensorimotor neuropathy (1 subject each) in the 2.7 mg/kg group; and febrile neutropenia and septic shock (1 subject each) in the 3.6 mg/kg group.

4.(iv).(3) Foreign phase I study (Study SG035-0002)

Adverse events were reported by 4 of 4 subjects (100%) in the 0.4 mg/kg group, 4 of 4 subjects (100%) in the 0.6 mg/kg group, 6 of 6 subjects (100%) in the 0.8 mg/kg group, 12 of 12 subjects (100%) in the 1.0 mg/kg group, 12 of 12 subjects (100%) in the 1.2 mg/kg group, and 6 of 6 subjects (100%) in the 1.4 mg/kg group, and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 3 of 4 subjects (75%) in the 0.4 mg/kg group, 4 of 4 subjects (100%) in the 0.6 mg/kg group, 6 of 6 subjects (100%) in the 0.8 mg/kg group, 12 of 12 subjects (100%) in the 1.0 mg/kg group, 12 of 12 subjects (100%) in the 1.2 mg/kg group, and 6 of 6 subjects (100%) in the 1.4 mg/kg group. Adverse events with an incidence of ≥20% in any group were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.13.0)	Number of subjects (%)											
	0.4 mg/kg group		0.6 mg/kg group		0.8 mg/kg group		1.0 mg/kg group		1.2 mg/kg group		1.4 mg/kg group	
	N = 4		N = 4		N = 6		N = 12		N = 12		N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	4 (100)	4 (100)	1 (25)	6 (100)	2 (33)	12 (100)	5 (42)	12 (100)	7 (58)	6 (100)	5 (83)
Gastrointestinal disorders												
Nausea	1 (25)	1 (25)	0	0	3 (50)	0	7 (58)	0	6 (50)	0	5 (83)	0
Diarrhoea	1 (25)	0	0	0	2 (33)	0	4 (33)	1 (8)	6 (50)	0	1 (17)	1 (17)
General disorders and administration site conditions												
Fatigue	0	0	2 (50)	0	4 (67)	0	5 (42)	1 (8)	8 (67)	0	4 (67)	0
Pyrexia	0	0	1 (25)	0	1 (17)	0	2 (17)	0	5 (42)	0	2 (33)	0
Infections and infestations												
Upper respiratory tract infection	0	0	1 (25)	0	1 (17)	0	2 (17)	0	4 (33)	0	2 (33)	0
Metabolism and nutrition disorders												
Decreased appetite	0	0	0	0	1 (17)	0	5 (42)	0	2 (17)	0	2 (33)	0
Musculoskeletal and connective tissue disorders												
Arthralgia	2 (50)	0	2 (50)	0	2 (33)	0	2 (17)	0	3 (25)	0	1 (17)	0
Myalgia	0	0	0	0	1 (17)	0	1 (8)	0	5 (42)	0	3 (50)	0
Nervous system disorders												
Peripheral sensory neuropathy	2 (50)	0	2 (50)	0	5 (83)	1 (17)	7 (58)	0	9 (75)	2 (17)	4 (67)	3 (50)

Serious adverse events were reported by 1 of 4 subjects (25%) in the 0.4 mg/kg group, 1 of 4 subjects (25%) in the 0.6 mg/kg group, 1 of 6 subjects (17%) in the 0.8 mg/kg group, 2 of 12 subjects (17%) in the 1.0 mg/kg group, 2 of 12 subjects (17%) in the 1.2 mg/kg group, and 3 of 6 subjects (50%) in the 1.4 mg/kg group. The reported serious adverse events were vomiting and nausea (1 subject each) in the 0.4 mg/kg group; hypoxia (1 subject) in the 0.6 mg/kg group; pneumonia influenzal and catheter site infection (1 subject each) in the 0.8 mg/kg group; diarrhoea, hyperglycaemia, vomiting, electrolyte imbalance, and neutropenia (1 subject each) in the 1.0 mg/kg group; pneumonia influenzal, pneumonia bacterial, and urinary tract infection (1 subject each) in the 1.2 mg/kg group; and diarrhoea, hyperglycaemia, peripheral motor neuropathy, and peripheral sensory neuropathy (1 subject each) in the 1.4 mg/kg group. Of these, a causal relationship to brentuximab vedotin could not be ruled out for diarrhoea, hyperglycaemia, electrolyte imbalance, neutropenia, and vomiting (1 subject each) in the 1.0 mg/kg group, and diarrhoea, hyperglycaemia, peripheral motor neuropathy, and peripheral sensory neuropathy (1 subject each) in the 1.4 mg/kg group.

Adverse events leading to treatment discontinuation of brentuximab vedotin were reported by 2 of 6 subjects (33%) in the 0.8 mg/kg group, 3 of 12 subjects (25%) in the 1.0 mg/kg group, 3 of 12 subjects (25%) in the 1.2 mg/kg group, and 5 of 6 subjects (83%) in the 1.4 mg/kg group. The reported adverse events leading to treatment discontinuation of brentuximab vedotin were peripheral sensory neuropathy and peripheral motor neuropathy (1 subject each) in the 0.8 mg/kg group; peripheral sensory neuropathy, hepatic enzyme increased, and vomiting (1 subject each) in the 1.0 mg/kg group; peripheral sensory neuropathy (2 subjects) and pneumonia influenzal (1 subject) in the 1.2 mg/kg group; and peripheral sensory neuropathy (2 subjects), peripheral motor neuropathy, chills, and myalgia (1 subject each) in the 1.4 mg/kg group. Of these, a causal relationship to brentuximab vedotin could not be ruled out for peripheral sensory neuropathy and peripheral motor neuropathy (1 subject each) in the 0.8 mg/kg group; peripheral sensory

neuropathy, hepatic enzyme increased, and vomiting (1 subject each) in the 1.0 mg/kg group; peripheral sensory neuropathy (2 subjects) in the 1.2 mg/kg group; and peripheral sensory neuropathy (2 subjects), peripheral motor neuropathy, chills, and myalgia (1 subject each) in the 1.4 mg/kg group.

4.(iv).(4) Foreign phase II study (Study SG035-0003)

Adverse events were reported by 100 of 102 subjects (98%), and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 94 of 102 subjects (92%). Adverse events with an incidence of ≥20% were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.13.0)	Number of subjects (%) N = 102	
	All Grades	Grade ≥3
All adverse events	100 (98)	56 (55)
Blood and lymphatic system disorders		
Neutropenia	22 (22)	20 (20)
Gastrointestinal disorders		
Nausea	43 (42)	0
Diarrhoea	37 (36)	1 (< 1)
Vomiting	22 (22)	0
General disorders and administration site conditions		
Fatigue	47 (46)	2 (2)
Pyrexia	30 (29)	2 (2)
Infections and infestations		
Upper respiratory tract infection	38 (37)	0
Nervous system disorders		
Peripheral sensory neuropathy	48 (47)	9 (9)
Respiratory, thoracic and mediastinal disorders		
Cough	21 (21)	0

Serious adverse events were reported by 25 of 102 subjects (25%). The reported serious adverse events were abdominal pain, demyelinating polyneuropathy, pneumonitis, pneumothorax, pulmonary embolism, pyelonephritis, and pyrexia (2 subjects each), and abdominal pain upper, bronchitis, candidiasis, cellulitis, diabetic coma, diarrhoea, diffuse large B-cell lymphoma, flank pain, gastrointestinal haemorrhage, H1N1 influenza, haematemesis, haemoptysis, HL, hyperglycaemia, intestinal perforation, lung infection, mental status changes, muscular weakness, nausea, peripheral motor neuropathy, pleural effusion, PCP, pneumonia, septic shock, soft tissue infection, staphylococcal bacteraemia, SJS, thrombocytopenia, urinary tract infection staphylococcal, and wrist fracture (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for pyrexia and demyelinating polyneuropathy (2 subjects each), and thrombocytopenia, abdominal pain, haematemesis, PCP, pneumonia, staphylococcal bacteraemia, hyperglycaemia, muscular weakness, peripheral motor neuropathy, mental status changes, pneumonitis, pulmonary embolism, and SJS (1 subject each).

Adverse events leading to treatment discontinuation of brentuximab vedotin were reported by 20 of 102 subjects (20%). The reported adverse events leading to treatment discontinuation of brentuximab vedotin were peripheral sensory neuropathy (6 subjects), peripheral motor neuropathy (3 subjects), HL (2 subjects), and arthralgia, demyelinating polyneuropathy, dermatitis allergic, muscular weakness, myelodysplastic syndrome, pneumonitis, pulmonary embolism, SJS, and throat tightness (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for peripheral sensory neuropathy (5 subjects), peripheral motor neuropathy (3 subjects), and arthralgia, demyelinating polyneuropathy, dermatitis allergic, muscular weakness, pneumonitis, pulmonary embolism, SJS, and throat

tightness (1 subject each).

4.(iv).(5) Foreign phase II study (Study SG035-0004)

Adverse events were reported by 58 of 58 subjects (100%), and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 53 of 58 subjects (91%). Adverse events with an incidence of ≥20% were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.13.0)	Number of subjects (%) N = 58	
	All Grades	Grade ≥3
All adverse events	58 (100)	36 (62)
Blood and lymphatic system disorders		
Neutropenia	12 (21)	12 (21)
Gastrointestinal disorders		
Nausea	23 (40)	1 (2)
Diarrhoea	17 (29)	2 (3)
Constipation	13 (22)	1 (2)
General disorders and administration site conditions		
Fatigue	22 (38)	3 (5)
Pyrexia	20 (34)	1 (2)
Nervous system disorders		
Peripheral sensory neuropathy	24 (41)	7 (12)
Skin and subcutaneous tissue disorders		
Rash	14 (24)	0

Serious adverse events were reported by 25 of 58 subjects (43%). The reported serious adverse events were ALCL (3 subjects), ventricular arrhythmia, pain in extremity, septic shock, and urinary tract infection (2 subjects each), and abdominal pain, acute myocardial infarction, anaemia, asthenia, atrial fibrillation, atrioventricular block complete, bradycardia, cellulitis, constipation, decreased appetite, deep vein thrombosis, demyelinating polyneuropathy, diarrhoea, encephalopathy, endocarditis staphylococcal, fluid overload, gastroenteritis viral, gastrointestinal haemorrhage, generalised oedema, haemorrhage intracranial, hydronephrosis, hypercalcaemia, klebsiella bacteraemia, lower limb fracture, mental status changes, mycosis fungoides, myositis, neuralgia, neutropenia, peripheral motor neuropathy, peripheral sensory neuropathy, pneumonia, pulmonary embolism, pulmonary oedema, rash papular, renal failure, acute kidney injury, respiratory failure, retinal vein occlusion, spinal cord compression, sudden death, superinfection bacterial, syncope, tracheal disorder, tumour flare, tumour lysis syndrome, and vomiting (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for urinary tract infection (2 subjects), and neutropenia, retinal vein occlusion, constipation, diarrhoea, vomiting, pneumonia, tumour lysis syndrome, myositis, tumour flare, demyelinating polyneuropathy, neuralgia, peripheral motor neuropathy, peripheral sensory neuropathy, and pulmonary embolism (1 subject each).

Adverse events leading to treatment discontinuation of brentuximab vedotin were reported by 16 of 58 subjects (28%), including peripheral sensory neuropathy (6 subjects), and retinal vein occlusion, sudden death, transaminases increased, ALCL, demyelinating polyneuropathy, haemorrhage intracranial, neuralgia, renal failure, acute kidney injury, and dermatitis (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for peripheral sensory neuropathy (5 subjects), and retinal vein occlusion, transaminases increased, demyelinating polyneuropathy, neuralgia, and dermatitis (1 subject each).

4.(iv).(6) Foreign phase I study (Study SGN35-007)

Adverse events were reported by 52 of 52 subjects (100%), and adverse events for which a causal relationship to brentuximab vedotin could not be ruled out were reported by 46 of 52 subjects (88%). Adverse events with an incidence of ≥20% were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.13.0)	Number of subjects (%) N = 52	
	All Grades	Grade ≥3
All adverse events	52 (100)	31 (60)
Blood and lymphatic system disorders		
Neutropenia	11 (21)	9 (17)
Gastrointestinal disorders		
Nausea	20 (38)	1 (2)
Vomiting	12 (23)	2 (4)
Diarrhoea	12 (23)	0
General disorders and administration site conditions		
Fatigue	20 (38)	1 (2)
Pyrexia	20 (38)	0
Infections and infestations		
Upper respiratory tract infection	11 (21)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	11 (21)	0
Nervous system disorders		
Peripheral sensory neuropathy	26 (50)	5 (10)
Respiratory, thoracic and mediastinal disorders		
Cough	13 (25)	0
Dyspnoea	12 (23)	3 (6)

Serious adverse events were reported by 19 of 52 subjects (37%). The reported serious adverse events were pyrexia (4 subjects), HL (3 subjects), dyspnoea, hypoxia, muscular weakness, nausea, peripheral sensory neuropathy, pneumonia, and vomiting (2 subjects each), and anaemia, anaphylaxis, ankle fracture, axonal neuropathy, bone pain, bradycardia, cardio-respiratory arrest, chest discomfort, clostridium test positive, cytomegalovirus viraemia, dehydration, demyelinating polyneuropathy, device related infection, duodenal ulcer, febrile neutropenia, femur fracture, hepatic encephalopathy, hyperbilirubinaemia, hyperglycaemia, hyperhidrosis, methaemoglobinaemia, pancytopenia, pericardial effusion, peripheral motor neuropathy, pleural effusion, pruritus, radiation pneumonitis, renal failure, respiratory distress, respiratory failure, and urticaria (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for peripheral sensory neuropathy, dyspnoea, hypoxia, and pyrexia (2 subjects each), and axonal neuropathy, hepatic encephalopathy, peripheral motor neuropathy, chest discomfort, febrile neutropenia, pancytopenia, bradycardia, nausea, vomiting, hyperbilirubinaemia, anaphylaxis, hyperglycaemia, hyperhidrosis, pruritus, and urticaria (1 subject each).

Adverse events leading to treatment discontinuation of brentuximab vedotin were reported by 8 of 52 subjects (15%). The reported adverse events leading to treatment discontinuation of brentuximab vedotin were peripheral sensory neuropathy (4 subjects), and axonal neuropathy, thrombocytopenia, asthenia, and blood creatinine increased (1 subject each). Of these, a causal relationship to brentuximab vedotin could not be ruled out for peripheral sensory neuropathy (3 subjects).

4.(iv).(7) Foreign phase I study (Study SGN35-008A)

Adverse events were reported by 19 of 19 subjects (100%) in the A-ket group, 14 of 16 subjects (88%) in the A-mid group, and 20 of 21 subjects (95%) in the A-rif group, and adverse events for

which a causal relationship to brentuximab vedotin could not be ruled out were reported by 15 of 19 subjects (79%) in the A-ket group, 12 of 16 subjects (75%) in the A-mid group, and 17 of 21 subjects (81%) in the A-rif group. Adverse events with an incidence of ≥20% in any group were as shown in the following table.

Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA ver.13.0)	Number of subjects (%)					
	A-ket group		A-mid group		A-rif group	
	N = 19		N = 16		N = 21	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	19 (100)	9 (47)	14 (88)	4 (25)	20 (95)	9 (43)
Blood and lymphatic system disorders						
Neutropenia	3 (16)	3 (16)	1 (6)	0	7 (33)	7 (33)
Gastrointestinal disorders						
Nausea	9 (47)	0	2 (13)	0	6 (29)	0
Diarrhoea	6 (32)	0	3 (19)	0	4 (19)	0
General disorders and administration site conditions						
Fatigue	8 (42)	0	3 (19)	1 (6)	5 (24)	0
Pyrexia	7 (37)	1 (5)	0	0	6 (29)	0
Nervous system disorders						
Headache	4 (21)	0	4 (25)	0	5 (24)	0

Serious adverse events were reported by 5 of 19 subjects (26%) in the A-ket group, 2 of 16 subjects (13%) in the A-mid group, and 3 of 21 subjects (14%) in the A-rif group. The reported serious adverse events were deep vein thrombosis, myelitis transverse, respiratory tract infection, pyrexia, staphylococcal infection, intestinal obstruction, and clostridium difficile colitis (1 subject each) in the A-ket group, constipation, dehydration, failure to thrive, enterocolitis, gastrointestinal haemorrhage, hepatic necrosis, abdominal pain, ALT increased, AST increased, haematemesis, nausea, and vomiting (1 subject each) in the A-mid group, and febrile neutropenia, atrial fibrillation, pancytopenia, cytomegalovirus infection, haemorrhage intracranial, pneumonia, and septic shock (1 subject each) in the A-rif group. Of these, a causal relationship to the study drug could not be ruled out for deep vein thrombosis, respiratory tract infection, and pyrexia (1 subject each) in the A-ket group, enterocolitis, gastrointestinal haemorrhage, hepatic necrosis, abdominal pain, ALT increased, AST increased, haematemesis, nausea, and vomiting (1 subject each) in the A-mid group, and febrile neutropenia, pancytopenia, cytomegalovirus infection, haemorrhage intracranial, pneumonia, and septic shock (1 subject each) in the A-rif group.

Adverse events leading to treatment discontinuation of the study drug were not reported other than 1 death during the study period.

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

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

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2-5). As a result, protocol deviations (non-compliance with the rules for examinations) were found at some clinical trial sites. Although the inspection identified the deviations that should be corrected, appropriate actions were taken for the relevant patients. PMDA therefore concluded that the clinical studies have generally been conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that a certain level of efficacy of brentuximab vedotin in patients with relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma has been demonstrated and that its safety is acceptable based on the observed clinical benefits. Brentuximab vedotin is a drug with a new active ingredient. Brentuximab vedotin binds to CD30 and is internalized into cells via CD30 in the form of an antibody-drug conjugate. Inside cells, MMAE is released by proteolytic cleavage and induces cell cycle arrest and apoptosis, resulting in inhibition of tumor proliferation. Thus, brentuximab vedotin has a clinical significance as a treatment option for relapsed or refractory CD30-positive Hodgkin's lymphoma and anaplastic large-cell lymphoma. The proposed indications, dosage and administration, and post-marketing investigations will be further discussed at the Expert Discussion.

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

Review Report (2)

November 5, 2013

I. Product Submitted for Registration

[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 22, 2013

II. Content of the Review

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

(1) Efficacy

As a result of the review described in "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA concluded that a certain level of efficacy of Brentuximab Vedotin (Genetical Recombination) (hereinafter referred to as "brentuximab vedotin") has been demonstrated in patients with relapsed or refractory CD30-positive Hodgkin's lymphoma (HL) or patients with relapsed or refractory CD30-positive systemic anaplastic large-cell lymphoma (sALCL), for both of which no standard treatment is available, because brentuximab vedotin showed efficacy in a Japanese phase I/II study (Study TB-BC010088) and foreign phase II studies (Studies SG035-0003 and SG035-0004).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

(2) Safety

As a result of the review described in "4.(iii).B.(3) Safety" of the Review Report (1), PMDA concluded that adverse events requiring attention during treatment with brentuximab vedotin were infusion reaction, neuropathy peripheral, bone marrow depression, infections, progressive multifocal leukoencephalopathy (PML), tumour lysis syndrome (TLS), Stevens-Johnson syndrome (SJS), lung disorders, and pancreatitis acute, and that attention should be paid to these adverse events in using brentuximab vedotin. In addition, in view of the above points, PMDA concluded that brentuximab vedotin is tolerable, provided that monitoring and managing of adverse events as well as dose delay, dose reduction, discontinuation, etc., are performed appropriately by physicians with sufficient knowledge and experience of chemotherapy for haematopoietic malignancies when using brentuximab vedotin.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. Besides, the following comments were raised from the expert advisors:

- Since conditions (prior therapies, tumor burden at the start of treatment) of patients eligible for brentuximab vedotin therapy may substantially vary among individuals, adverse events should be monitored and controlled carefully, especially during the early post-marketing phase.

- Collaboration with physicians specializing in neurology, dermatology, respiratory medicine etc. is important in order to manage adverse events such as neuropathy peripheral, PML, SJS, and lung disorders. Brentuximab vedotin should be used at a medical institution where

adequate collaboration with these physicians could be available in the event of an emergency so as to ensure early and appropriate actions against the above adverse events.

- Because of difficulty in specifying symptoms etc. associated with adverse events of lung disorders reported from foreign post-marketing experience, it is necessary to review not only the incidences but also the timing of onset of the individual adverse events and risk factors such as the presence of pulmonary complications, and to appropriately provide the derived information to healthcare professionals.

Taking account of comments from the Expert Discussion, PMDA asked the applicant to explain the timing of onset of and risk factors for lung disorders reported from foreign post-marketing experience.

The applicant responded as follows:
In total, 22 patients experienced lung disorders for which a causal relationship to brentuximab vedotin could not be ruled out (data cutoff date, [redacted], 20[redacted]) [see "4.(iii).B.(3).9) Lung disorders" of the Review Report (1)] and the events occurred in 7 patients after dosing of Cycle 2, in 3 patients after dosing of Cycle 3, in 1 patient each after dosing of Cycles 1, 4, 5, 6, 8, and 9, and in 6 patients at an unknown time point, showing no consistent tendency in the timing of onset of these events. A total of 10 of 22 patients had received prior chemotherapy with bleomycin hydrochloride (bleomycin) and 6 of 22 patients had prior or current infection(s), but definite risk factors for brentuximab vedotin-related lung disorders are unknown.

PMDA considers as follows:
Monitoring and managing of adverse events requiring attention during treatment with brentuximab vedotin should be performed carefully according to the patient's condition such as prior therapies and disease stage at the start of treatment and in collaboration with physicians specializing in neurology, dermatology, respiratory medicine etc. depending on the observed adverse events; this information should be appropriately disseminated and caution should be exercised appropriately using information materials.

In addition, given the fact that definite risk factors for brentuximab vedotin-related lung disorders are unknown, at present, information should be appropriately provided using relevant materials regarding the details of each lung disorder reported to date including the timing of onset and lung complications in these cases.

PMDA instructed the applicant to take appropriate actions regarding the above issues, and the applicant agreed to accept the instruction.

After the submission of the application, it was decided to issue precautionary statements regarding pancreatitis acute in view of foreign post-marketing spontaneous reports and other data. In addition, while the compilation of the Review Report (1) was in progress, PMDA asked the applicant to check for the occurrence of adverse events requiring precautions other than pancreatitis acute.

The applicant responded to the inquiry as follows:
The occurrence of brentuximab vedotin-related adverse events has been periodically reviewed in collaboration with US Seattle Genetics, Inc. and Millennium Inc. based on information such as foreign post-marketing spontaneous reports, resulting in the necessity of precautions against hepatic function disorder based on the information as of [redacted], 20[redacted]. As for hepatic function disorder, 17 of 84 patients who experienced liver disorders (Standardised MedDRA query ver.16) died, and causes of these deaths included disease progression in 9 patients, graft versus host disease in 3 patients, and idiopathic pulmonary syndrome after haematopoietic stem cell

transplantation, sepsis, alcohol abuse, hepatitis fulminant, cardiomegaly/cardiac failure/pulmonary oedema/steatohepatitis in 1 patient each (data cutoff date, August 18, 2013). A causal relationship to brentuximab vedotin could not be ruled out for hepatic encephalopathy/hyperbilirubinaemia reported by 1 patient who died of disease progression, hepatitis fulminant/transaminases increased reported by 1 patient who died of hepatitis fulminant, and hepatomegaly reported by 1 patient who died of cardiomegaly/cardiac failure/pulmonary oedema/steatohepatitis.

The pharmacokinetic (PK) parameters of brentuximab vedotin and monomethyl auristatin E (MMAE) in patients with hepatic or renal impairment who received brentuximab vedotin at a dose of 1.2 mg/kg every 3 weeks in a foreign phase I study (Study SGN35-008B, December 2009 to ongoing) were as shown in the table below (data cutoff date, [redacted], 20[redacted]). Although hepatic impairement and renal impairment had no apparent effects on the exposure to brentuximab vedotin, the geometric mean ratios (patients with hepatic impairment/patients with normal hepatic function) for C_{max} and $AUC_{0-\infty}$ of MMAE were 1.2 to 2.8 and 1.8 to 3.5, respectively, and the geometric mean ratios (patients with severe renal impairment/patients with normal renal function) for C_{max} and $AUC_{0-\infty}$ of MMAE were 2.1 and 1.9, respectively. Previously, there seemed little need to adjust the dose of brentuximab vedotin in patients with renal or hepatic impairment [see "4.(ii).A.(7) Effects of function kidney decreased and function liver decreased on PK of brentuximab vedotin and MMAE" of the Review Report (1)]. However, based on the above findings, the applicant considered that 1.2 mg/kg of brentuximab vedotin should be selected as the initial dose in patients with hepatic impairement or severe renal impairment. Results of the final analysis of the above study will be available in [redacted] 20[redacted].

PK parameters of brentuximab vedotin and MMAE in patients with hepatic or renal impairment (data cutoff date, [redacted], 20[redacted])

	Normal[*1]	Severity of hepatic impairment[*2]			Severity of renal impairment[*3]		
		Mild	Moderate	Severe	Mild	Moderate	Severe
n	8	1	5	1	4	3	3
Brentuximab vedotin							
C_{max} (μg/mL)	23.39 (28)	20.70	18.93 (19)	18.70	18.78 (28)[*4]	24.44 (12)	17.37 (20)
$AUC_{0-\infty}$ (μg·day/mL)	51.39 (19)	29.26	33.47 (61)	46.62	44.66 (45)[*4]	62.55 (21)	36.57 (31)
MMAE							
C_{max} (ng/mL)	4.05 (75)	11.30	6.59 (54)	4.92	3.15 (95)	3.73 (28)	8.38 (17)
$AUC_{0-\infty}$ (ng·day/mL)	27.23 (80)	95.49	60.30 (71)	48.08	23.10 (79)	29.61 (41)	51.65 (39)

Geometric mean (CV%); *1, Results obtained from patients receiving brentuximab vedotin alone (at a dose of 1.2 mg/kg every 3 weeks) in the A-ket group in a foreign phase I study (Study SGN35-008A) [see "4.(ii).A.(4) Foreign phase I study" of the Review Report (1)] (8 patients with both normal hepatic and renal functions, out of 19 patients); *2, "Mild," "Moderate," and "Severe" were defined as Child-Pugh Class A, B, and C, respectively; *3, "Mild," "Moderate," and "Severe" were defined as creatinine clearance of >50 and ≤80, ≥30 and ≤50, and <30 mL/min, respectively; *4, n = 3

Regarding safety in Study SGN35-008B, all of the 17 subjects enrolled into the study received brentuximab vedotin and were included in the safety analysis population. Deaths were observed in 4 subjects during the study period, and causes of these deaths included myocardial infarction in 1 subject with renal impairment (enrolled as a patient with severe renal impairment) and brain herniation, lower respiratory tract infection fungal, and cryptococcal fungaemia in 1 subject each with hepatic impairment (enrolled as patients of Child-Pugh Class B, B, and C, respectively; PS was 3 in all of the 3 patients). A causal relationship to brentuximab vedotin was ruled out for all events. The applicant explained that the patient with lower respiratory tract infection fungal had experienced respiratory distress 24 days after administration of brentuximab vedotin (a total of 1

dose) and died 26 days after the administration due to fungal infectious disorders (zygomycosis), and that the patient with cryptococcal fungaemia had tested positive for *Cryptococcus neoformans* on a peripheral blood culture collected 2 days after administration of brentuximab vedotin (a total of 1 dose) and died 6 days after the administration due to cryptococcal fungaemia.

PMDA considers as follows:
Approximately half of patients in Studies SG035-0003, SG035-0004, and TB-BC010088 showed a worsening trend in liver function tests [see "4.(iii).B.(3).11).(a) Hepatic function disorder" of the Review Report (1)] and that there have been reports of serious events of hepatic function disorder including hepatitis fulminant after administration of brentuximab vedotin that resulted in death. Therefore attention should be paid to occurrence of hepatic function disorder through measures including periodic liver function tests. Thus, precautionary statements should be appropriately included in the package insert etc. about available information on the incidence of hepatic function disorder including hepatitis fulminant reported to date.

Study SGN35-008B showed increased exposure to MMAE in patients with hepatic impairment or severe renal impairment. The pooled data from foreign phase I studies and foreign phase II studies suggested that tumor response obtained with brentuximab vedotin may correlate more strongly with exposure to brentuximab vedotin than with that to MMAE [see "4.(ii).A.(8).1) Relationship between exposure and efficacy" of the Review Report (1)]. Based on the above findings, there has been no clinical pharmacological evidence to select 1.2 mg/kg of brentuximab vedotin as the initial dose in patients with hepatic impairment or severe renal impairment. However, the severity of neutropenia tended to increase in patients with high MMAE exposure [see "4.(ii).A.(8).2) Relationship between exposure and safety" of the Review Report (1)], and therefore, appropriate precautionary statements should be issued about the increased exposure to MMAE in patients with hepatic impairment or severe renal impairment.

In Study SGN35-008B, death due to fungal infection occurred in a patient with moderate hepatic impairment and another patient with severe hepatic impairment; this information should be appropriately disseminated. In addition, whether or not brentuximab vedotin may be used in patients with moderate or severe hepatic impairment should be carefully decided due to the above findings as well as the following reasons:

- Infection is an important identified risk of brentuximab vedotin [see "(5) Risk management plan (draft)"].

- The increased exposure to MMAE observed in patients with hepatic impairment suggests that an increased exposure to MMAE may cause fatal adverse events, including infections, in patients with moderate or severe hepatic impairment.

Based on the above, PMDA concluded that the following statements should be included in the warnings and the Precautions for Dosage and Administration sections, and that information on the pharmacokinetic data from Study SGN35-008B should be included in the Pharmacokinetics section of the package insert. In addition, information on the final analysis of the ongoing Study SGN35-008B should be appropriately disseminated when the results are available.

[Warnings]
- 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.

[Precautions for dosage and administration]
- Since blood concentrations of monomethyl auristatin E (MMAE; a component of brentuximab vedotin) may increase in patients with hepatic impairment or severe renal impairment, dose reduction should be considered. These patients should be closely monitored and caution should be exercised for occurrence of adverse events.

PMDA instructed the applicant to take appropriate actions regarding the above issues, and the applicant accepted the instruction.

(3) Clinical positioning and indication

As a result of the review described in "4.(iii).B.(4) Clinical positioning" and "4.(iii).B.(5) Indication" of the Review Report (1), PMDA concluded that brentuximab vedotin is positioned as a treatment option for patients with relapsed or refractory CD30-positive HL and sALCL. Therefore, the following proposed indications are considered appropriate when the precautionary statements shown below are included in the Precautions for Indications section of the package insert.

[Indications]
The following relapsed or refractory CD30-positive diseases:
Hodgkin's lymphoma, anaplastic large-cell lymphoma

[Precautions for 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 patients who are confirmed to be positive for CD30 antigen with the immunohistological or other appropriate methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to include the above statements in the Indication and the Precautions for Indications sections, and the applicant accepted the instruction.

(4) Dosage and administration

As a result of the review described in "4.(iii).B.(6) Dosage and administration" of the Review Report (1), PMDA concluded that the proposed dosage and administration is acceptable with the following precautionary statements in the Precautions for Dosage and Administration section.

[Dosage and administration]
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.

[Precautions for dosage and administration]
- The efficacy and safety of concomitant use of brentuximab vedotin with other antineoplastic drugs have not been established.

- Preparation of injectable solution and infusion duration: Reconstitute the contents of one vial with 10.5 mL of Water for Injection (JP), and dilute a suitable volume with Isotonic Sodium Chloride Solution (JP) or 5% Glucose Injection (JP) to make a 0.4 to 1.2 mg/mL solution. The diluted solution should be intravenously infused over at least 30 minutes.

- If an adverse drug reaction occurred after administration of brentuximab vedotin, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Criteria for dose delay, dose reduction, and discontinuation in patients with neuropathy peripheral

NCI-CTCAE 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 neuropathy improves to Grade ≤1 or baseline. If the patient has recovered, 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

Criteria for dose delay, dose reduction, and discontinuation in patients with neutropenia

NCI-CTCAE Grade *	Measures
Grade 1 (<LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)	Continue dosing at the same dose regimen.
Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)	Hold dosing until neutropenia improves to Grade ≤2 or baseline. If the patient has recovered, resume treatment at the same dose regimen.

LLN, Lower limit of normal; *, Based on NCI-CTCAE v3.0

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to include the above statements in the dosage and administration and the Precautions for Dosage and Administration sections, and the applicant accepted the instruction.

(5) Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance covering all patients with relapsed or refractory CD30-positive HL or anaplastic large-cell lymphoma treated with brentuximab vedotin in order to confirm the safety etc. of brentuximab vedotin under routine use. The planned sample size is 140 as an analysis population. The observation period will be 16 cycles from the start of treatment. The proposed priority investigation items for the post-marketing surveillance are neuropathy peripheral, infections, neutropenia, and infusion reaction.

As a result of its review in "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1), PMDA concluded that the post-marketing surveillance should be conducted, taking account of the paucity of currently available safety information on brentuximab vedotin in Japanese patients and the need to promptly collect the relevant information. The priority investigation items, analytical sample size, and observation period of the post-marketing surveillance are acceptable as proposed by the applicant's plan.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. In addition, the following comments were raised from the expert advisors:

- As lung disorders, pneumonitis (including interstitial lung disease) for which a causal relationship to brentuximab vedotin could not be ruled out were reported from foreign post-marketing experience. Although such events were not reported by Japanese patients in clinical studies, given the very limited number of evaluated Japanese patients, lung disorders should be added to the priority investigation items of the post-marketing surveillance.

- It is necessary to collect information on history and details of premedication such as antiviral drugs and ST combinations for prevention of infections such as herpes virus infection and pneumocystis jiroveci pneumonia.

- Information on the following is crucial: occurrence of adverse events such as graft versus host disease and infections after administration of brentuximab vedotin in patients who have undergone a haematopoietic stem cell transplant (SCT); and impact of SCT on the safety of brentuximab vedotin etc. In addition, patients may undergo SCT after administration of brentuximab vedotin, but information on safety in such patients is limited. Therefore, it is necessary to collect information on whether patients have undergone SCT before or after administration of brentuximab vedotin, wherever possible, through the post-marketing surveillance.

Taking account of comments from the Expert Discussion, PMDA instructed the applicant to amend the risk management plan as follows, and the applicant accepted the instruction.

- To add lung disorders to the priority investigation items of the post-marketing surveillance.

- To collect information on history of antiviral drug medication for prevention of infections.

- To collect information on whether patients have undergone SCT before or after administration of brentuximab vedotin.

A foreign phase III study (Study SGN35-005) is ongoing in patients with CD30-positive HL at high risk for relapse due to residual disease after autologous haematopoietic stem cell transplant. Results of the study will become available in [redacted], 20[redacted]. PMDA instructed the applicant to appropriately provide this information upon receipt, and the applicant accepted the instruction.

Taking account of the above discussion, PMDA concluded that the proposed risk management plan for brentuximab vedotin should include the following safety and efficacy specifications, additional pharmacovigilance activities, survey/study on efficacy, and risk minimization activities, as shown in the tables below.

Safety and efficacy specifications of risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Peripheral neuropathy • Infections • PML • Bone marrow depression • Infusion reaction • TLS • SJS • Lung disorders • Pancreatitis acute • Hepatic function disorder	• Reproductive toxicity • Depletion of thymic lymphoid tissue • Interactions with CYP3A4 inhibitors	None
Efficacy specification		
• Efficacy under routine use of brentuximab vedotin		

Summary of additional pharmacovigilance activities, plans of survey/study on efficacy, and risk minimization activities in risk management plan

Additional pharmacovigilance activities	Survey/study on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing surveillance (all-case surveillance)	• Post-marketing surveillance (all-case surveillance)	• Information provision via early post-marketing phase vigilance • Preparation and distribution of information materials for healthcare professionals to ensure proper use

Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety etc. of brentuximab vedotin under routine use
Survey method	All-case surveillance
Population	Patients with relapsed or refractory CD30-positive HL and anaplastic large-cell lymphoma
Observation period	16 cycles from the start of treatment
Planned sample size	140 patients
Priority investigation items	Neuropathy peripheral, infections, neutropenia, infusion reaction, and lung disorders

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the following indication and dosage and administration with the following conditions for approval, provided that appropriate precautionary statements will be included in the package insert, that information on the proper use of brentuximab vedotin will be disseminated appropriately after the market launch, and that brentuximab vedotin will be used properly under the supervision of a physician with sufficient knowledge and experience in chemotherapy for haematopoietic malignancies, at a medical institution well equipped to cope with emergencies. The re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indications] The following relapsed or refractory CD30-positive diseases: Hodgkin's lymphoma, anaplastic large-cell lymphoma

[Dosage and administration] 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.

[Conditions for approval] The applicant is required to:
Conduct a drug use-results survey involving all treated patients after the market launch until data from a certain number of patients have been accumulated, in order to understand the characteristics of patients treated with this product, since only a limited number of Japanese patients participated in clinical studies of the product. At the same time, collect safety and efficacy data on the product without delay and take necessary measures for the proper use of the product.

[Warnings]

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 haematopoietic 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]

1. Patients with a history of severe hypersensitivity to any ingredients of the product

2. Patients who are receiving bleomycin

[Precautions for indications]

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 patients who are confirmed to be positive for CD30 antigen with the immunohistological or other appropriate methods. The positivity of CD30 should be verified by pathologists or laboratories with sufficient experience.

[Precautions for dosage and administration]

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

2. Preparation of injectable solution and infusion duration: Reconstitute the contents of one vial with 10.5 mL of Water for Injection (JP), and dilute a suitable volume with Isotonic Sodium Chloride Solution (JP) or 5% Glucose Injection (JP) to make a 0.4 to 1.2 mg/mL solution. The diluted solution should be intravenously infused over at least 30 minutes.

3. Since blood concentrations of monomethyl auristatin E (MMAE; a component of brentuximab vedotin) increase in patients with hepatic impairment or severe renal impairment, dose reduction should be considered. These patients should be closely monitored and caution should be exercised for occurrence of adverse events.

4. If an adverse drug reaction occurred after administration of brentuximab vedotin, patients should have dose delay, dose reduction, or discontinuation by referring to the following criteria:

Peripheral neuropathy

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 neuropathy improves to Grade ≤1 or baseline. If the patient has recovered, 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

Neutropenia

Grade*	Measures
Grade 1 (<LLN and ≥1500/mm^3) or Grade 2 (<1500 and ≥1000/mm^3)	Continue dosing at the same dose regimen.
Grade 3 (<1000 and ≥500/mm^3) or Grade 4 (<500/mm^3)	Hold dosing until neutropenia improves to Grade ≤2 or baseline. If the patient has recovered, resume treatment at the same dose regimen.

LLN, Lower limit of normal; *, Based on NCI-CTCAE v3.0