Report on the Deliberation Results

April 25, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Blenrep for I.V. Infusion 100 mg
Non-proprietary Name	Belantamab Mafodotin (Genetical Recombination) (JAN*)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 13, 2024

Results of Deliberation

In its meeting held on April 21, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Latest Corrected Version**

Review Report

April 9, 2025

Pharmaceuticals and Medical Devices Agency

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

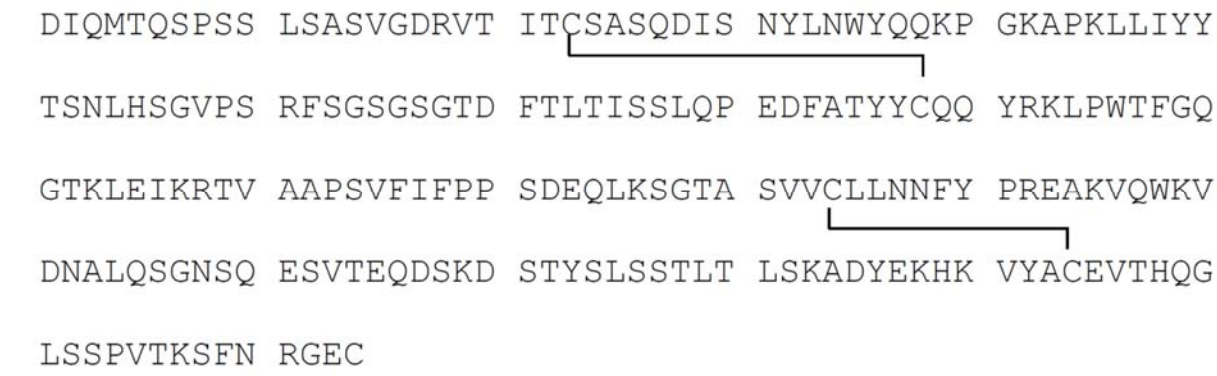
Brand Name	Blenrep for I.V. Infusion 100 mg
Non-proprietary Name	Belantamab Mafodotin (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 13, 2024
Dosage Form/Strength	Lyophilized powder for injection, each vial containing 110 mg of belantamab mafodotin (genetical recombination)
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Belantamab Mafodotin is an antibody-drug-conjugate (molecular weight: ca. 152,000) consisting of Mafodotin (*N*- ((2*R*,3*R*)-3-{(2*S*)-1-[(3*R*,4*S*,5*S*)-4-({*N*-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]-*N*-methyl-L-valyl-Lvalyl}methylamino)-3-methoxy-5-methylheptanoyl]pyrrolidin-2-yl}-3-methoxy-2-methylpropanoyl)-L-phenylalanine ($C_{49}H_{76}N_6O_{11}$; molecular weight: 925.16)), which is composed of monomethylauristatin F and linker, attached to an average of 4 Cys residues of a recombinant monoclonal antibody. The monoclonal antibody moiety is an anti-human B cell manutation antigen (BCMA) monoclonal antibody, the complementarity-determining regions of which are derived from mouse antibody and other regions are derived from human IgG1 and produced in glycoprotein 6-α-L-fucosyltransferase-deficient Chinese hamster ovary cells. The protein moiety is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

** The English translation has been corrected to reflect the corrections listed in the latest errata sheet (dated December 18, 2025) for the Japanese original.

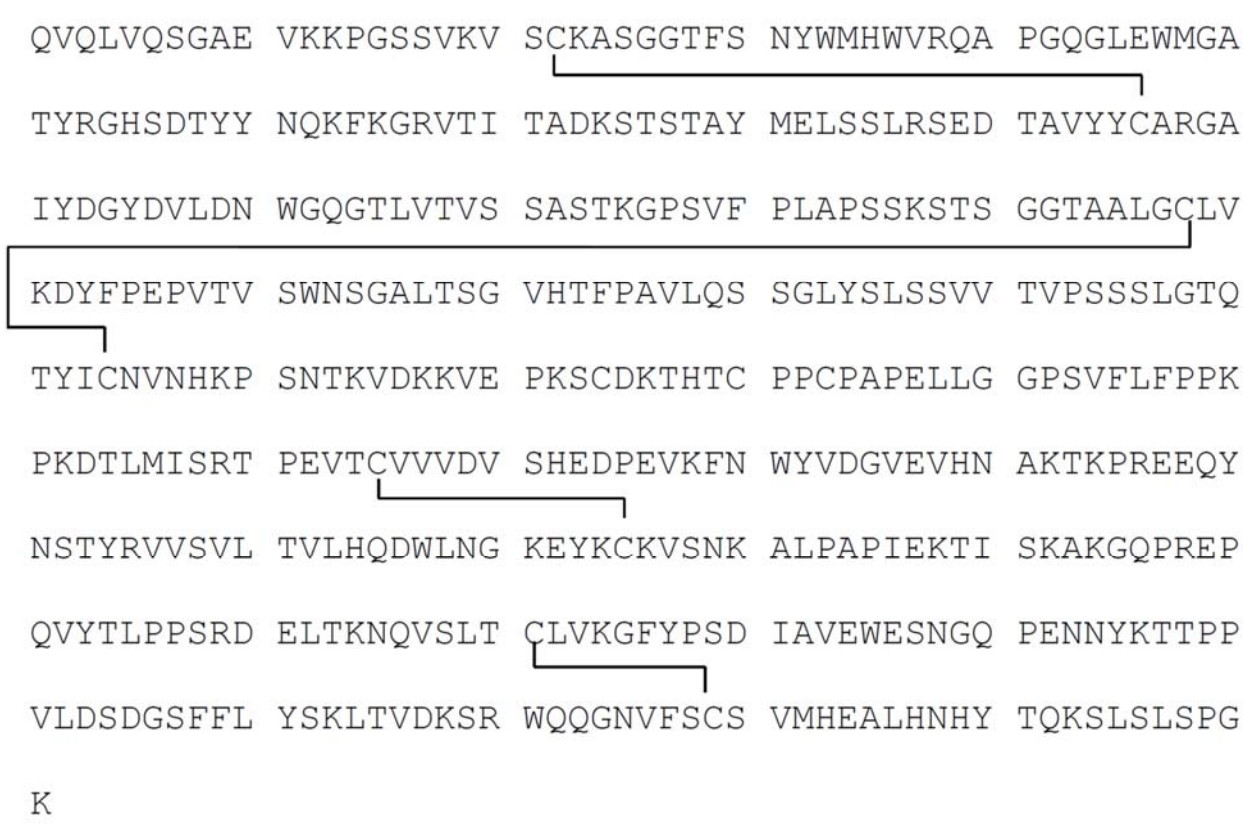
Structure

Amino acid sequence:

Light (L) chain



Heavy (H) chain



Intra-chain disulfide bonds: solid lines

Inter-chain disulfide bonds: L-chain C214–H-chain C224, H-chain C230–H-chain C230, H-chain C233–H-chain C233

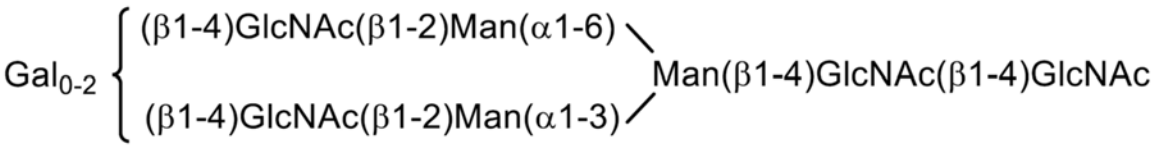
Pyroglutamic acid: H-chain Q1

Glycosylation: H-chain N301

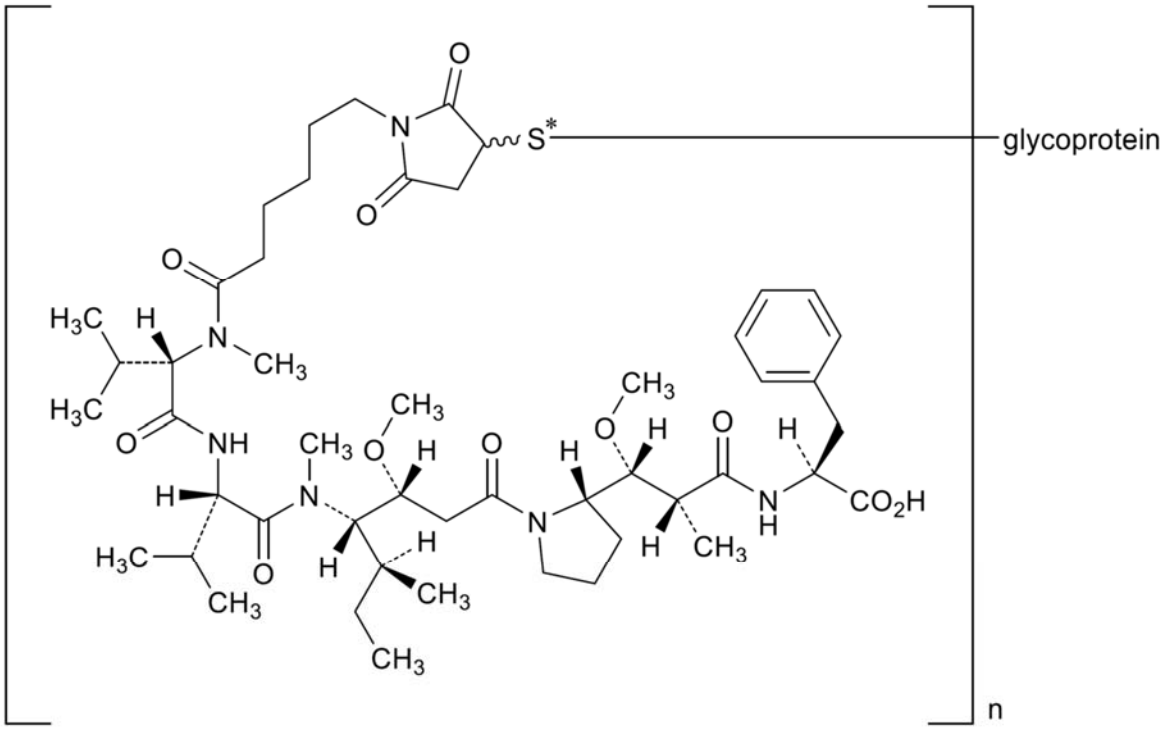
Partial processing: H-chain K451

Potential drug binding site: L-chain C214, H-chain C224, H-chain C230, and H-chain C233

Main proposed carbohydrate structure



Structural formula of mafodotin



On average, n = 4

* indicates a sulfur atom of a cysteine residue in the antibody moiety

Molecular formula: $C_{6484}H_{10008}N_{1728}O_{2030}S_{44}$ (protein moiety, 4 chains)

Molecular weight: Approximately 152,000

Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 623 of 2024 [*R6 yaku*]; PSB/PED Notification No. 0828-9, dated August 28, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of relapsed or refractory multiple myeloma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

The following events should be investigated further through post-marketing surveillance: gastrointestinal disorders, bleeding, and infusion reaction.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

In combination with bortezomib and dexamethasone:

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg administered as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition.

In combination with pomalidomide and dexamethasone:

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second dose, administered as an intravenous infusion over at least 30 minutes every 4 weeks. The dose should be reduced depending on the patient's condition.

Approval Conditions

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

Latest Corrected Version

Attachment

Review Report (1)

March 7, 2025

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

Product Submitted for Approval

Brand Name	Blenrep for I.V. Infusion 100 mg
Non-proprietary Name	Belantamab Mafodotin (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 13, 2024
Dosage Form/Strength	Lyophilized powder for injection, each vial containing 110 mg of belantamab mafodotin (genetical recombination)

Proposed Indication

Relapsed or refractory multiple myeloma

Proposed Dosage and Administration

In combination with bortezomib and dexamethasone

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg administered as an intravenous infusion every 3 weeks. The dose should be reduced or withheld depending on the patient's condition.

In combination with pomalidomide and dexamethasone

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second and subsequent doses, administered as an intravenous infusion every 4 weeks. The dose should be reduced or withheld depending on the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

B-cell maturation antigen (BCMA) is expressed on normal B-lineage cells, and it has been reported that its expression increases when B cells are differentiated into plasma blasts and bone marrow plasma cells, as well as by transformation of plasma cells into malignant cells (*J Immunol*. 2007;179:7276-86, *Immunotherapy*. 2015;7:1187-99).

Belantamab mafodotin is an antibody-drug conjugate (ADC) developed by GlaxoSmithKline in the US, and consists of belantamab, human immunoglobulin G1 (IgG1) subclass anti-BCMA humanized monoclonal antibody, that is covalently conjugated via a peptide linker to monomethyl auristatin F (MMAF), a tubulin polymerization inhibitor.

Belantamab mafodotin binds to BCMA expressed on the tumor cell membrane. Upon internalization into the cell, free cysteine maleimidocaproyl MMAF (cys-mcMMAF) is released from the antibody component, which is thought to induce apoptosis and other effects, leading to inhibition of tumor growth.

1.2 Development history, etc.

A foreign phase I study (DREAMM-1 study) was conducted by GlaxoSmithKline in patients with relapsed or refractory multiple myeloma (MM) from July 2014. Thereafter, global phase III studies were conducted in patients with relapsed or refractory MM by the GlaxoSmithKline Research & Development Limited in the UK: the DREAMM-7 study from May 2020 and DREAMM-8 study from October 2020.

In the US and European Union (EU), applications were filed in [redacted] 20[redacted] and in [redacted] 20[redacted], respectively, for the combination regimens of belantamab mafodotin for the treatment of relapsed or refractory MM: belantamab mafodotin in combination with bortezomib and dexamethasone (Bd) and belantamab mafodotin in combination with pomalidomide and dexamethasone (Pd). The applications are currently under review.

Earlier, belantamab mafodotin monotherapy was approved in the US and EU for the indications shown below. However, a global phase III study (DREAMM-3 study) [see Section 7.1.2.3] did not meet its primary endpoint of progression-free survival (PFS), showing no significant improvement in PFS in the belantamab mafodotin monotherapy compared with the control (Pd). Based on the results and other factors, approval was withdrawn in February 2023 in the US, while the EU issued a decision to not renew the conditional marketing authorization in February 2024.

(1) US (accelerated approval was granted in August 2020): BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

(2) EU (conditional marketing authorization was granted in August 2020): Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

As of February 2025, belantamab mafodotin has not been approved in any country or region for the indication of relapsed or refractory MM.

In Japan, the applicant started enrollment of participants for the DREAMM-7 and DREAMM-8 studies in June 2021 and January 2022, respectively.

Recently, the applicant filed an application for marketing approval of belantamab mafodotin based on data from the DREAMM-7 and DREAMM-8 studies as pivotal data.

Belantamab mafodotin was designated as an orphan drug (Orphan Drug Designation No. 623 of 2024 [*R6 yaku*]) with the intended indication of "multiple myeloma" in August 2024.

2. Quality and Outline of the Review Conducted by PMDA

Belantamab mafodotin is an ADC composed of belantamab, a monoclonal antibody targeting BCMA, that is conjugated to mcMMAF (SGD-1269), which consists of a tubulin polymerization inhibitor MMAF and a peptide linker.

2.1 Drug substance

[redacted] and [redacted] are controlled as critical intermediates of the drug substance.

2.1.1 Belantamab

2.1.1.1 Generation and control of cell substrate

[redacted] mouse was immunized with [redacted]. [redacted] cells from the immunized [redacted] mouse were fused with mouse [redacted] cells to generate hybridomas, and optimum clones were selected. The expression construct for belantamab was generated from [redacted] of [redacted] and [redacted] of [redacted] prepared via humanization, etc. based on the genetic sequence of the clone. The expression construct was transfected into Chinese hamster ovary (CHO) cells lacking the genes involved in fucose synthesis. The clone best suited to the manufacture of belantamab was selected to establish the master cell bank (MCB) and working cell bank (WCB).

Characterization and purity tests of the MCB, WCB, and end of production cell bank (EPCB) were performed in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines Q5A (R1), Q5B, and Q5D. The test results

demonstrated genetic stability during production. Within the range tested, no viral or non-viral adventitious agents were detected other than general endogenous retrovirus-like particles in CHO cell lines.

Both the MCB and WCB are stored in [redacted]. While there is no [redacted] MCB, the WCB may be [redacted] on an as-needed basis.

2.1.1.2 Manufacturing process

The manufacturing process of belantamab consists of the following steps: thawing of the WCB vial/culture expansion, culture expansion, production culture, harvest, [redacted] chromatography, [redacted] viral inactivation, [redacted] chromatography, virus removal filtration, [redacted]/final filtration by ultrafiltration/diafiltration, filling, and testing/storage.

[redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] [redacted] are defined as critical steps.

Process validation is performed [redacted] for the manufacturing process of belantamab.

2.1.1.3 Safety evaluation of adventitious agents

With the exception of CHO cells, the host cells, no raw materials of biological origin are used in the manufacturing process of belantamab.

Purity was tested on the MCB, WCB, and EPCB [see Section 2.1.1.1]. A mouse minute virus detection assay for [redacted], bioburden testing, mycoplasma testing, *in vitro* adventitious virus testing, and transmission electron microscopy were performed on a commercial scale. Within the range studied, the tests detected no contamination caused by viral or nonviral adventitious agents. These tests performed on [redacted], except for [redacted] and [redacted], were specified as in-process control tests.

The viral clearance study was performed using model viruses, and the results demonstrated that the purification process has a certain level of viral clearance capability (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Mouse minute virus	Pseudorabies virus	Reovirus type 3
[redacted] chromatography	[redacted]			
[redacted] viral inactivation				
[redacted] chromatography				
Virus removal filtration				
Overall virus reduction factor	≥18.43	≥13.52	≥15.27	≥11.44

2.1.1.4 Manufacturing process development

When the manufacturing processes were changed during the development of belantamab, comparability was evaluated in accordance with the ICH Q5E guideline, and the results demonstrated the comparability of belantamab before and after the change. Formulations produced from [redacted] were used in the clinical studies.

2.1.1.5 Characterization

2.1.1.5.1 Structure and characterization

Table 2 summarizes the characterization performed. Main evaluation results for biological properties are discussed in Section "2.1.3.3.1 Structure and characterization" together with the evaluation results of the drug substance.

Table 2. Evaluation items for characterization

Primary/higher order structure	Amino acid sequence, N- and C-terminal amino acid sequence, post-translational modifications ([redacted], [redacted], [redacted], and [redacted]), molecular weight, disulfide bonds, [redacted], [redacted], secondary structure, tertiary structure, thermal stability
Physicochemical properties	Size variants, charge variants
Glycan structure	N-linked glycan profile
Biological properties	BCMA binding affinity
	FcγR binding affinity (FcγRI, FcγRIIa [131R and 131H], FcγRIIIa [158V and 158F]), FcRn binding affinity
	Cell growth inhibitory activity
	ADCC activity, ADCP activity

2.1.1.5.2 Product-related substances/Product-related impurities

No product-related substances have been identified. Based on data including the characterization results in Section "2.1.1.5.1 Structure and characterization," Impurity A, Impurity B, Impurity C, and Impurity D were identified as product-related impurities. Of these, Impurity A, Impurity C, and Impurity D are controlled by the specifications for [redacted], [redacted], and [redacted], while Impurity B is controlled by the specifications for [redacted] and [redacted].

2.1.1.5.3 Process-related impurities

Host cell deoxyribonucleic acid (DNA), host cell protein (HCP), Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, Impurity L, Impurity M, Impurity N, and Impurity O were identified as process-related impurities. It has been verified that host cell DNA, HCP, Impurity E, Impurity F, Impurity G, and Impurity H are adequately removed in the manufacturing process. The other process-related impurities are considered to pose a low safety risk, either because the process knowledge suggests that they are adequately removed during the manufacturing process, or because their maximum exposure is lower than the allowable daily exposure. Impurity P is controlled by the specifications for belantamab.

2.1.1.6 Control of belantamab

The proposed specifications for belantamab include content, description, identification (surface plasmon resonance [SPR]), [redacted], pH, osmolality, purity (size exclusion chromatography [SEC] and capillary isoelectric focusing [cIEF]), Impurity P, bacterial endotoxins, microbial limit, biological activity ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.1.1.7 Stability of belantamab

Table 3 shows main stability studies for belantamab.

Table 3. Summary of main stability studies for belantamab

	Number of batches*1	Storage condition	Study period	Storage container
Long-term	3	[redacted] ± [redacted] °C	[redacted] months*2	[redacted]
Accelerated	3	[redacted] ± [redacted] °C	[redacted] months	
Stress	3	[redacted] ± [redacted] °C	[redacted] months	
		[redacted] ± [redacted] °C/[redacted] ± [redacted] % RH	[redacted] months	
		[redacted] ± [redacted] °C/[redacted] ± [redacted] % RH	[redacted] months	
Photostability	1	Overall illumination of ≥[redacted] lux·h and an integrated near ultraviolet energy of ≥[redacted] W·h/m^2		

*1, [redacted]; *2, the stability test is ongoing and will be continued for up to [redacted] months

The long-term, accelerated, and stress tests ([redacted] ± [redacted]°C and [redacted] ± [redacted]°C/[redacted] ± [redacted]% RH) did not reveal any clear changes in quality attributes throughout the study period.

The stress test ([redacted] ± [redacted]°C/[redacted] ± [redacted]% RH) showed [redacted] in [redacted] and [redacted] in [redacted]; [redacted] in [redacted] and [redacted] in [redacted] in [redacted]; and [redacted] in [redacted].

The results of the photostability test showed that belantamab was photo[redacted].

Based on the above results, a shelf life of [redacted] months was proposed for belantamab when stored in [redacted] at [redacted] [redacted].

2.1.2 mcMMAF (SGD-1269)

2.1.2.1 Characterization

Maleimidocaproyl MMAF (SGD-1269), which consists of a peptide linker and MMAF, is a white solid. Its description, crystalline form, melting point, hygroscopicity, solubility, optical rotation, and ultraviolet-visible absorption spectra have been determined.

The chemical structure of mcMMAF (SGD-1269) has been elucidated by ^{1}H- and ^{13}C-nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), and infrared absorption spectroscopy (IR).

2.1.2.2 Manufacturing process

Maleimidocaproyl MMAF (SGD-1269) is synthesized using the following starting materials (1) to (6).

(1) [redacted][1)]
(2) [redacted]
(3) [redacted][2)]
(4) [redacted][3)]
(5) [redacted][4)]
(6) [redacted][5)]

Based on the following analyses, a quality control strategy was developed (Table 4).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on the quality risk assessment and consideration of the proven acceptable range (PAR) for the process parameters

Table 4. Outline of control strategy for mcMMAF (SGD-1269)

CQA	Control method
Identification	Specifications
Purity*	Manufacturing process, specifications
Content	Manufacturing process, specifications

*, Including related substances (bound related substances)

[redacted] step by [redacted], and [redacted] step by [redacted], [redacted] and [redacted], and [redacted] are defined as critical steps. Process control items and values are specified for the [redacted] step.

2.1.2.3 Control of mcMMAF (SGD-1269)

The proposed specifications for mcMMAF (SGD-1269) include content, description, identification (IR and high performance liquid chromatography [HPLC]), purity tests (related substances [HPLC], purity [HPLC], [redacted], [redacted], and residual solvents [gas chromatography (GC)]), water content, and assay (HPLC).

1) [redacted]
2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]
6) [redacted]
7) [redacted]
8) [redacted]
9) [redacted]

2.1.2.4 Stability of mcMMAF (SGD-1269)

Table 5 shows the main stability studies for mcMMAF (SGD-1269). The results demonstrated that mcMMAF (SGD-1269) is stable. The photostability study showed that mcMMAF (SGD-1269) is photo[redacted].

Table 5. Summary of main stability studies for SGD-1269

Study	Number of batches	Temperature	Storage container	Storage period
Long-term	[redacted]: 3 batches	[redacted] ± [redacted]℃	[redacted] + [redacted]*1+ [redacted]	[redacted] months
Accelerated		[redacted] ± [redacted]℃	[redacted] + [redacted]	[redacted] months
		[redacted] ± [redacted]℃*2		[redacted] months

*1, [redacted] containing [redacted] [redacted]; *2, humidity was [redacted] ± [redacted]% RH

Based on the above results, a retest period of [redacted] months has been proposed for mcMMAF (SGD-1269) when placed in [redacted] with [redacted] [redacted] [redacted], then in [redacted] with [redacted], and stored at [redacted], [redacted].

2.1.3 Belantamab mafodotin (genetical recombination)

2.1.3.1 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: [redacted], [redacted], [redacted], [redacted], filtration, filling [redacted], and testing/storage.

[redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process.

2.1.3.2 Manufacturing process development

When the manufacturing processes were changed during the development of the drug substance, comparability was evaluated in accordance with the ICH Q5E guideline, and the results demonstrated the comparability of the drug substance before and after the change. Formulations produced from [redacted] were used in the clinical studies.

2.1.3.3 Characterization

2.1.3.3.1 Structure and characterization

Table 6 summarizes the characterization performed.

Table 6. Evaluation items for characterization

Primary/higher order structure	Amino acid sequence, N- and C-terminal amino acid sequence, molecular weight, post-translational modifications ([redacted], [redacted], [redacted], [redacted]), [redacted], disulfide bonds, [redacted], secondary structure, tertiary structure, thermal stability
Physicochemical properties	Size variants, charge variants, [redacted], [redacted]
Glycan structure	N-linked glycan profile
Biological properties	BCMA binding affinity
	FcγR binding affinity (FcγRI, FcγRIIa [131R and 131H], FcγRIIIa [158V and 158F]), FcRn binding affinity
	Cell growth inhibitory activity
	ADCC activity, ADCP activity

Key investigation results for the biological properties of the drug substance and belantamab are as shown below.

- The cell growth inhibitory activity of belantamab and the drug substance was investigated in an adenosine triphosphate (ATP) assay of live cells using the human MM cell lines (OPM-2 and MOLP-8). While belantamab showed no cell growth inhibitory activity, the drug substance exhibited dose-dependent cell growth inhibitory activity.
- The antibody dependent cell-mediated cytotoxicity (ADCC) activity of belantamab and the drug substance was investigated by reporter assays based on luciferase activity using Jurkat cells expressing Fcγ receptor (FcγR)IIIa and expressing, under the control of a nuclear factor of activated T-cells (NFAT) promotor, luciferase, as effector cells, with the NCI-H929 human MM cell line as the target cells. The results indicated that belantamab and the drug substance had ADCC activity.
- The antibody dependent cell-mediated phagocytosis (ADCP) activity of belantamab was investigated by reporter assays based on luciferase activity using Jurkat cells expressing FcγRIIa and expressing, under the control of an NFAT promotor, luciferase, as effector cells, with the ARH77 human MM cell line as the target cells. The ADCP activity of the drug substance was investigated in a test in which target cells engulfed by macrophages were detected using CD11b[10)] and PKH67[11)] double staining as indicators, with healthy adult macrophages as effector cells and human MM cells labeled with PKH67 as the target cells. The results indicated that belantamab and the drug substance had ADCP activity.

2.1.3.3.2 Product-related substances/Product-related impurities

No product-related substances have been identified. Based on data including the characterization results in Section "2.1.3.3.1 Structure and characterization," Impurity A, Impurity B, Impurity C, Impurity D, and Impurity Q were identified as product-related impurities. Of these, Impurity A, Impurity D, and Impurity C are controlled by the specifications for [redacted], [redacted], and [redacted], Impurity B is controlled by the specifications for [redacted] and [redacted], and Impurity Q is controlled by the specifications for [redacted].

10) A macrophage marker
11) A fluorescent dye, which can stain the cell membrane

2.1.3.3.3 Process-related impurities

Impurity R, Impurity S, Impurity T, Impurity U, and Impurity V were identified as process-related impurities. It has been verified that Impurity T, Impurity U, and Impurity V are adequately removed in the manufacturing process. It is known that the maximum exposure of Impurity R is lower than the allowable daily exposure, and Impurity S is used as an intravenous formulation in other countries at a dose level higher than the level used in the manufacturing process. Therefore, the impurities are considered to pose a low safety risk.

2.1.3.4 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (SPR and peptide mapping), pH, osmolality, purity (SEC, capillary gel electrophoresis [CGE; non-reducing and reducing conditions], , and cIEF), , bacterial endotoxins, microbial limit, biological activity (, , and), and assay (ultraviolet-visible spectrophotometry).

2.1.3.5 Stability of drug substance

Table 7 shows main stability studies for the drug substance.

Table 7. Summary of main stability studies for the drug substance

	Number of batches*1	Storage condition	Study period	Storage container
Long-term	4	± °C	months*2	
Accelerated	4	± °C	months	
Stress	4	± °C	months	
		± °C/ ± % RH	months	
		± °C/ ± % RH	months	
Photostability	1	Overall illumination of ≥ lux·h and an integrated near ultraviolet energy of ≥ W·h/m^2		

*1, The drug substance that was with using ; *2, the stability test is ongoing up to months

The long-term, accelerated, and stress tests (± °C) did not reveal any clear changes in quality attributes throughout the study period.

The stress test (± °C/ ± % RH) showed the following: in in ; in and in in ; in ( ) in ; and in .

On the other hand, the stress test (± °C/ ± % RH) showed the following: in and in in ; in , in , and in in ; in ( ) in ; in ; and in .

The results of the photostability test showed that the drug substance was photo.

Based on the above results, a shelf life of [redacted] months was proposed for the drug substance when stored in [redacted] at [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized powder for injection, and each glass vial (10 mL) contains 110 mg of belantamab mafodotin. The drug product contains, as excipients, sodium citrate hydrate, citric acid hydrate, trehalose hydrate, disodium edetate hydrate, and polysorbate 80. Each vial is filled with an excess volume of belantamab mafodotin compared to the labeled amount so that, following reconstitution with 2 mL of water for injection (the resulting belantamab mafodotin concentration is 50 mg/mL), 100 mg of belantamab mafodotin can be obtained.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], filtration sterilization, filling [redacted], lyophilization, crimping/inspection/testing, labeling/packaging/testing, and storage steps.

[redacted] are defined as critical steps.

Process validation is performed on a commercial scale for the manufacturing process of the drug product.

2.2.3 Manufacturing process development

When the manufacturing processes were changed during the development of the drug product, comparability was evaluated in accordance with the ICH Q5E guideline, and the results demonstrated the comparability of the drug product before and after the change. Formulations [redacted] were used in the clinical studies.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (SPR), pH, osmolality, purity (SEC, CGE [reducing condition], and cIEF), foreign insoluble matter, insoluble particulate matter, water content, reconstitution time, uniformity of dosage units, bacterial endotoxins, sterility, biological activity ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 8 shows main stability studies for the drug product.

Table 8. Summary of main stability studies for the drug product

	Number of batches*	Storage condition	Study period	Storage container
Long-term	3	5 ± 3°C	60 months	[redacted] rubber stopper and glass vial
Accelerated	3	25 ± [redacted]°C/60 ± [redacted]% RH	6 months	
Stress	2	40 ± [redacted]°C/75 ± [redacted]% RH	6 months	
Photostability	1	Overall illumination of ≥[redacted] lux·h and an integrated near ultraviolet energy of ≥[redacted] W·h/m^2		

*, The formulation was [redacted] with [redacted] using [redacted]

The long-term, accelerated, and stress tests did not reveal any clear changes in quality attributes throughout the study period.

The results of the photostability test showed that the drug product was photostable.

Based on the above results, a shelf life of 60 months was proposed for the drug product when stored at 2°C to 8°C using [redacted] rubber stopper and a glass vial as the primary container.

2.3 Quality control strategy

Based on the analyses shown below, a quality control strategy was developed. The control strategy consists of control of the raw materials, manufacturing procedure, and process parameters, process monitoring, in-process control testing, specifications, and characterization studies [for product-related impurities and process-related impurities, see Sections 2.1.5.2, 2.1.5.3, 2.1.3.3.2, and 2.1.3.3.3].

- Identification of CQAs

  The following CQAs were identified based on the information obtained during the development of belantamab mafodotin and related knowledge.

  CQAs: description (appearance of powder; and color and turbidity of liquid), foreign insoluble matter, insoluble particulate matter, pH, osmolality, protein content, [redacted], [redacted], [redacted], [redacted], [redacted] ([redacted], [redacted], and [redacted]), virus, microbiological safety, (bioburden, bacterial endotoxins, sterility, and mycoplasma), [redacted], reconstitution time, water content, uniformity of dosage units, [redacted], [redacted], [redacted], and [redacted], [redacted] ([redacted]), [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted]

- Process characterization

Based on the process characterization and process risk assessment, process parameters that influence CQAs and their permissible ranges were determined. The control strategy was also re-examined.

2.R Outline of the review conducted by PMDA

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

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity for BCMA (CTD 4.2.1.1-7)

The binding affinity of belantamab mafodotin for human or cynomolgus monkey BCMA (recombinant protein) was assessed by SPR. The K_D value (n = 1, individual value) of belantamab mafodotin was 8.357 nmol/L for human BCMA and 3.982 nmol/L for cynomolgus monkey BCMA.

3.1.2 Binding affinity for FcγR and FcRn (CTD 4.2.1.1-7)

The binding affinity of belantamab mafodotin, belantamab, and wild-type fucosylated anti-BCMA antibody[12)] for human FcγR (FcγRI, FcγRIIa-131R, FcγRIIa-131H, FcγRIIIa-158V, FcγRIIIa-158F), human neonatal Fc receptor (FcRn), and cynomolgus monkey FcγRs (FcγRIIa, FcγRIIb, and FcγRIII) (recombinant proteins) was evaluated by SPR. Table 9 shows the K_D values of belantamab mafodotin, belantamab, and wild-type fucosylated anti-BCMA antibody for human FcγR, human FcRn, cynomolgus monkey FcγR.

Table 9. Binding affinity of belantamab mafodotin, belantamab, or wild-type fucosylated anti-BCMA antibody for FcγR and FcRn

	K_D (nmol/L) (individual value)								
	Human						Cynomolgus monkey		
	FcγRI*1	FcγRIIa -131R*1	FcγRIIa -131H*1	FcγRIIIa -158V*1	FcγRIIIa -158F*1	FcRn*2	FcγRIIa*1	FcγRIIb*1	FcγRIII*1
Belantamab mafodotin	6.81	3,080	2,940	28	235	52.10	2,840	2,410	61
Belantamab	15	2,760	2,350	16	156	35.70	2,510	2,040	41
Wild-type fucosylated anti-BCMA antibody	18	4,790	2,840	329	2,420	34.70	3,490	2,530	346

n = 1; *1, K_D values at pH7.4; *2, K_D values at pH6.0

3.1.3 Internalization into the cell (CTD 4.2.1.1-10)

The endosomal internalization of belantamab was evaluated using NCI-H929 human MM cells by immunofluorescence staining based on co-localization with an early endosome marker (endosomal antigen [EEA]). The results showed that after being localized on the cell membrane, belantamab was localized in the endosomes.

12) Because belantamab is afucosylated to enhance its binding affinity to Fcγ receptors, a wild-type, fucosylated anti-BCMA antibody before afucosylation was used as the control group.

3.1.4 Induction of apoptosis (CTD 4.2.1.1-8, 4.2.1.1-9)

The ability of belantamab mafodotin to induce apoptosis was evaluated using the human MM cell lines NCI-H929 and KMS-12-BM by flow cytometry measuring the expression level of cleaved caspase-3. The results demonstrated that belantamab mafodotin induced apoptosis.

The ability of belantamab mafodotin to induce cell arrest was evaluated using the human MM cell lines MM1Sluc and RPMI8226 by flow cytometry with propidium iodide (PI) staining as an indicator. The results showed that G2/M arrest was induced by belantamab mafodotin in both MM cell lines.

3.1.5 ADCC activity (CTD 4.2.1.1-1)

The human MM cell line ARH77 stably expressing human BCMA labeled with fluorescent europium was co-cultured with healthy adult peripheral blood mononuclear cells (PBMC). The ADCC activity of belantamab mafodotin, belantamab, and wild-type fucosylated anti-BCMA antibody was evaluated based on europium levels in the cell culture as an indicator. The ARH77 cells treated with belantamab mafodotin, belantamab, or wild-type fucosylated anti-BCMA antibody for 30 minutes were co-cultured with PBMC for 2 hours, and fluorescence intensity in the cell culture fluid was measured. Table 10 shows the EC_{50} values for belantamab mafodotin, belantamab, and wild-type fucosylated anti-BCMA antibody.

Table 10. ADCC activity of belantamab mafodotin, belantamab, and wild-type fucosylated anti-BCMA antibody

	n	EC_{50} (ng/mL)
Belantamab mafodotin	1	1.8
Belantamab	2	1.6, 0.72
Wild-type fucosylated anti-BCMA antibody	2	32.2, 25.9

3.1.6 ADCP activity (CTD 4.2.1.1-8)

Using the human MM cell lines INA6, RPMI8226, and H929, labeled with PKH67,[11)] and macrophages obtained by inducing differentiation of healthy adult human monocytes by stimulating with macrophage-colony stimulating factor (M-CSF), the ADCP activity of belantamab mafodotin and the control ADC[13)] was evaluated by flow cytometry using CD11b[11)] and PKH67 double staining as indicators. Each human MM cell line was co-cultured with macrophages for 4 hours in the presence of belantamab mafodotin and the control ADC. The percentage of macrophages that engulfed the human MM cells, represented by positivity of CD11b and PKH67, was measured by flow cytometry. The ADCP activity in the belantamab mafodotin group was statistically significant compared with that in the control ADC group.

3.1.7 Effects on immune system (CTD 4.2.1.1-34)

The NCI-H929 human MM cells, mouse lymphoma EL4 cells, and EL4-hBCMA cells, which are EL4 cells expressing human BCMA, were treated with belantamab mafodotin. The expression levels of

13) An ADC conjugated with an IgG1 isotype antibody, which does not bind to human, monkey, or rat proteins, conjugated by a protease-resistant maleimidocaproyl (mc) linker to an MMAF

immune response markers (high-mobility group box 1 [HMGB1] and calreticulin [CRT]) and endoplasmic reticulum stress markers (heat shock protein70 [HSP70] and heat shock protein90α [HSP90α]) were evaluated by flow cytometry. In NCI-H929 and EL4-hBCMA cells, the expression of HMGB1, CRT, and endoplasmic reticulum stress markers from live cells increased in the belantamab mafodotin group compared with the belantamab group and the control ADC[13)] group. In EL4 cells, however, belantamab mafodotin treatment had no effect on CRT expression levels.

3.1.8 Inhibition of malignant tumor cell growth

3.1.8.1 *In vitro* (CTD 4.2.1.1-2, 4.2.1.1-13, 4.2.1.1-16)

The inhibitory effects of belantamab mafodotin on the growth of NCI-H929 and JJN3 human MM cells were evaluated using ATP from live cells as an indicator. The mean IC_{50} of belantamab mafodotin (95% confidence interval [CI]) (n = 3) was 8.9 ng/mL [8.0, 9.8] and 25.1 ng/mL [18.2, 34.8] for NCI-H929 and JJN3, respectively.

The effects of belantamab mafodotin on the cell viability of EL4 cells and EL4-hBCMA cells were evaluated using ATP from live cells as an indicator. The viability of EL4-hBCMA cells tended to decrease in a belantamab mafodotin concentration-dependent manner while the viability of EL4 cells was unaffected by belantamab mafodotin.

The effects of belantamab mafodotin on the cell viability of CD138-positive cells (plasma cells) derived from 3 MM patients were evaluated by flow cytometry using annexin V and PI staining. The viability of MM patient-derived CD138-positive cells tended to decrease in a belantamab mafodotin concentration-dependent manner.

3.1.8.2 *In vivo*

3.1.8.2.1 Belantamab mafodotin monotherapy (CTD 4.2.1.1-6, 4.2.1.1-8, 4.2.1.1-37)

The inhibitory effects of belantamab mafodotin on tumor growth were evaluated using xenograft severe combined immunodeficient (SCID) mice (N = 5/group) bearing subcutaneous NCI-H929 cells. Treatment was initiated on the day when the mean tumor volume reached approximately 200 mm^3 (Day 0). On Day 0, belantamab mafodotin or belantamab 50 or 100 µg (2 or 4 mg/kg) was administered intravenously twice weekly for 2 weeks, or control antibody[14)] or control ADC[13)] 100 µg was administered intravenously twice weekly for 2 weeks, and tumor volume was calculated. By Day 14, tumor growth inhibition was statistically significant in all belantamab groups and belantamab mafodotin groups compared with the control antibody group (Figure 1; $P < 0.05$ for all groups; testing with random coefficient regression models). In addition, the degree of tumor growth inhibition was statistically significant in all belantamab mafodotin groups compared with the same dose level in the belantamab group, the control antibody, and control ADC groups (Figure 1; $P < 0.05$ for all groups; tests by random coefficient regression models).

14) An IgG1 antibody that does not bind to human, monkey, or rat proteins

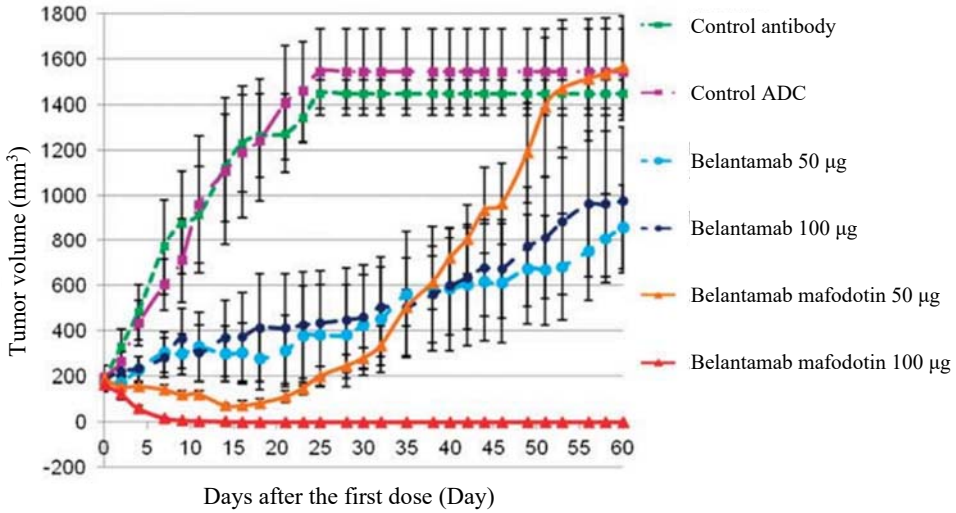


Figure 1. The inhibitory effects of belantamab mafodotin and belantamab in xenograft SCID mice bearing subcutaneous NCI-H929 cells
N = 5; mean ± standard error

The inhibitory effects of belantamab mafodotin on tumor growth were evaluated using xenograft SCID mice (N = 10/group) bearing subcutaneous NCI-H929 cells. Treatment was initiated on the day when the mean tumor volume reached 121 mm^3 (Day 0). Belantamab mafodotin 4 mg/kg was administered intraperitoneally on Day 0. Tumor volume on Day 24 and survival duration were calculated. The degree of tumor growth reduction was statistically significant in the belantamab mafodotin group compared with the vehicle (physiological saline) control group ($P = 0.000148$; Dunnett's multiple comparison test). The median survival duration in the belantamab mafodotin group and control (physiological saline) group was 34 days and 27 days, respectively.

The inhibitory effects of belantamab mafodotin on tumor growth were evaluated using xenograft SCID mice (N = 5/group) bearing subcutaneous OPM-2 human MM cells. Treatment was initiated on the day when the mean tumor volume reached approximately 200 mm^3 (Day 0). From Day 0, 100 µg (4 mg/kg) of belantamab mafodotin, belantamab, control antibody, [14] or control ADC[13] was administered intravenously twice weekly, for 1 or 2 weeks (2 or 4 doses in total), and the effects on tumor volume up to Day 14 were compared. The degree of tumor growth reduction was statistically significant in all belantamab mafodotin groups compared with the belantamab, control antibody, or control ADC groups (Figure 2; $P < 0.05$ for all groups; testing with random coefficient regression models). Tumor growth inhibition was not statistically significant in any of the belantamab groups compared with the control antibody group.

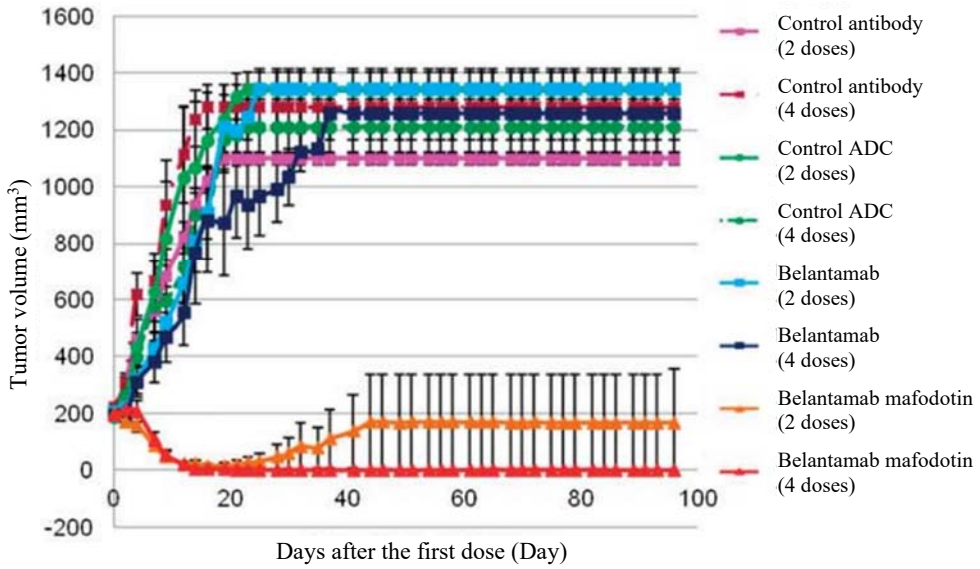


Figure 2. The inhibitory effects of belantamab mafodotin and belantamab in xenograft SCID mice bearing subcutaneous OPM-2 cells
N = 5; mean ± standard error

The inhibitory effects of belantamab mafodotin on tumor growth were evaluated using xenograft SCID mice (N = 8/group) bearing intravenous human MM1Sluc cells stably expressing luciferase. After intravenous injection of MM1Sluc cells in SCID mice, treatment was initiated on the day when the bioluminescence signal intensity reached 3,000,000 ph/s/cm^2/sr (Day 0). On Day 0, belantamab mafodotin 0.4 or 4 mg/kg, belantamab 4 mg/kg, or control ADC[13)] 4 mg/kg was administered intravenously twice weekly for a total of 9 doses, and tumor volume (bioluminescence signal) and survival duration were calculated. In all belantamab mafodotin groups and belantamab groups, a statistically significant reduction in tumor growth was shown compared with the vehicle (phosphate buffer saline [PBS]) control group and the control ADC group ($P < 0.05$ for all groups; Student's t-test). A statistically significant improvement in survival was also shown compared with the vehicle (PBS) control group and the control ADC group ($P \leq 0.0004$; log-rank test).

3.1.8.2.2 Belantamab mafodotin/Bd treatment (CTD 4.2.1.1-26)

The inhibitory effects of belantamab mafodotin alone and belantamab mafodotin in combination with bortezomib and dexamethasone (Bd) on tumor growth were evaluated using xenograft SCID mice (N = 10/group) bearing subcutaneous OPM-2 or MOLP-8 human MM cells. Treatment was initiated on the day when the mean tumor volume reached approximately 177 mm^3 (Day 0). From Day 0, the control ADC,[13)] belantamab mafodotin, bortezomib (BOR), and dexamethasone (DEX) were administered alone or in combination for 2 weeks as shown in Table 11, and tumor volume on Day 13 (OPM-2 tumor cells) or Day 16 (MOLP-8 tumor cells) was calculated. The control ADC, belantamab mafodotin, and BOR were administered twice weekly intraperitoneally, while DEX was administered QD intraperitoneally. Belantamab mafodotin/Bd tended to reduce tumor growth compared with belantamab mafodotin alone or Bd (Table 11).

Table 11. Tumor growth inhibition by belantamab mafodotin alone or belantamab mafodotin/Bd in SCID mouse xenograft models bearing subcutaneous MM cells

Treatment	Dose (mg/kg/dose)			Tumor volume (mm^3) (Mean ± standard error)	
	Belantamab mafodotin	BOR	DEX	OPM-2	MOLP-8
Vehicle control (physiological saline)	—	—	—	1,971 ± 100	1,288 ± 134
Control ADC (2 mg/kg)	—	—	—	1644 ± 93	933 ± 56
Belantamab mafodotin alone	2	—	—	562 ± 88*1	428 ± 54*1
BOR alone	—	1	—	1,350 ± 100*1	955 ± 78
DEX alone	—	—	3	1,455 ± 106*2	833 ± 126*2
Belantamab mafodotin in combination with BOR	2	1	—	285 ± 49*1, *3, *4	441 ± 63*1, *4
Belantamab mafodotin in combination with DEX	2	—	3	452 ± 47*1, *5	389 ± 54*1, *5
Bd	—	1	3	1,293 ± 77*1	885 ± 79*2
Belantamab mafodotin/Bd	2	1	3	269 ± 46*1, *3, *6	373 ± 62*1, *6

N = 10; *1, $P < 0.001$ (Independent-Samples t-test; the same applies hereinafter) compared with vehicle control (physiological saline); *2, $P < 0.05$ compared with vehicle control (physiological saline); *3, $P < 0.05$ compared with belantamab mafodotin alone; *4, $P < 0.05$ compared with BOR alone; *5, $P < 0.05$ compared with DEX alone; *6, $P < 0.05$ compared with Bd

3.1.8.2.3 Belantamab mafodotin/Pd treatment (CTD 4.2.1.1-26)

The inhibitory effects of belantamab mafodotin alone and belantamab mafodotin in combination with pomalidomide and dexamethasone (Pd) on tumor growth were evaluated using xenograft SCID mice (N = 10/group) bearing subcutaneous OPM-2 or MOLP-8 cells. Treatment was initiated on the day when the mean tumor volume reached approximately 178 mm^3 (for OPM-2 tumor cells) or approximately 160 mm^3 (for MOLP-8 tumor cells) (Day 0). From Day 0, the control ADC,[13)] belantamab mafodotin, DEX, or pomalidomide (POM) were administered alone or in combination for 2 weeks as shown in Table 12, and tumor volume on Day 10 (OPM-2 tumor cells) or Day 12 (MOLP-8 tumor cells) was calculated. While the control ADC and belantamab mafodotin were administered twice weekly intraperitoneally, DEX was administered QD intraperitoneally, and POM was administered QD orally. Belantamab mafodotin/Pd tended to reduce tumor growth compared with belantamab mafodotin alone or Pd (Table 12).

Table 12. Tumor growth inhibition by belantamab mafodotin alone or belantamab mafodotin/Pd in SCID mouse xenograft models bearing subcutaneous MM cells

Treatment	Dose (mg/kg/dose)			Tumor volume (mm^3) (Mean ± standard error)	
	Belantamab mafodotin	POM	DEX	OPM-2	MOLP-8
Control ADC (2 mg/kg)	—	—	—	1,358 ± 196	1,097 ± 133
Belantamab mafodotin alone	2	—	—	878 ± 93[*1]	633 ± 56[*1]
POM alone	—	2.5	—	730 ± 85[*1]	1,226 ± 140
DEX alone	—	—	3	1,264 ± 228	1166 ± 116
Belantamab mafodotin in combination with POM	2	2.5	—	597 ± 139[*1]	711 ± 58[*1, *3]
Pd	—	2.5	3	550 ± 92[*1]	931 ± 94
Belantamab mafodotin/Pd	2	2.5	3	355 ± 78[*1, *2]	646 ± 66[*1, *4]

N = 10; *1, $P < 0.05$ (Independent-Samples t-test; the same applies hereinafter) compared with control ADC; *2, $P < 0.05$ compared with belantamab mafodotin alone; *3, $P < 0.05$ compared with POM alone; *4, $P < 0.05$ compared with Pd

3.2 Secondary pharmacodynamics (CTD 4.2.1.1-3)

The inhibitory effects of belantamab on binding of human BCMA (recombinant protein) to B-cell activating factor (BAFF) or a proliferation-inducing ligand (APRIL) were evaluated by enzyme-linked immunosorbent assay (ELISA). The IC_{50} values (n = 1; individual values) of belantamab for BAFF and APRIL were 748.9 and 616.8 ng/mL, respectively.

The inhibitory effects of belantamab on the activation of nuclear factor κ B (NF-κB) by BAFF or by APRIL were evaluated using NCI-H929 human MM cells by ELISA measuring phosphorylated NF-κB. The IC_{50} values (n = 1) of belantamab for BAFF and APRIL were 0.91 and 2.43 μg/mL, respectively.

3.3 Safety pharmacology

3.3.1 Effects on central nervous system

Belantamab mafodotin 1, 3, or 10 mg/kg once every week (QW) was intravenously administered to cynomolgus monkeys (N = 6 or 10/group) in 3-week and 13-week repeated-dose toxicity studies to evaluate the effects of belantamab mafodotin on clinical signs. No effects of belantamab mafodotin were noted [see Section 5.2].

Belantamab mafodotin 3, 10, or 30 mg/kg QW was intravenously administered to rats (N = 30 or 32/group) in a 3-week repeated-dose toxicity study and belantamab mafodotin 3, 10, or 30 mg/kg once every 3 weeks (Q3W) was intravenously administered to rats (N = 24 or 36/group) in a 13-week repeated-dose toxicity study to evaluate the effects of belantamab mafodotin on clinical signs. No effects of belantamab mafodotin were noted [see Section 5.2].

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3-1)

Using the human embryonic kidney HEK293 cells transfected with human *ether-a-go-go* related gene (hERG), the effects of cys-mcMMAF[15)] on 10 or 100 μmol/L on hERG potassium current were evaluated. Cys-mcMMAF inhibited hERG current by 1.2% ± 0.7% or 3.4% ± 0.4% (mean ± standard error; N = 3 or 4), with the IC_{50} of cys-mcMMAF >100 μmol/L.

3.3.2.2 Effects on heart rate and electrocardiograms

Belantamab mafodotin 1, 3, or 10 mg/kg QW was intravenously administered to cynomolgus monkeys (N = 6 to 10/group) in 3-week and 13-week repeated-dose toxicity studies. In the 3-week repeated-dose toxicity study, effects of belantamab mafodotin on heart rate, electrocardiogram (RR, PR, QT, corrected QT [QTc], and QRS intervals), and blood cardiac troponin I concentration were evaluated, while in the 13-week repeated-dose toxicity study, effects of belantamab mafodotin on heart rate and electrocardiogram (RR, PR, QT, QTc, and QRS intervals) were evaluated. Both studies showed no effects of belantamab mafodotin on electrocardiograms or cardiac troponin I concentration. In the 13-week repeated-dose toxicity study, a 16% increase in heart rate was noted in 5 males at 10 mg/kg [see Section 5.2].

The applicant's explanation about the above results:
The C_{max} (302 μg/mL) in cynomolgus monkeys after administration of belantamab mafodotin 10 mg/kg QW was higher than the C_{max} of belantamab mafodotin (51.8 μg/mL) at the recommended clinical dose (2.5 mg/kg). Considering this and other factors, the above findings are unlikely to translate into safety concerns in the clinical use of belantamab mafodotin.

3.3.3 Effects on respiratory system

Belantamab mafodotin 1, 3, or 10 mg/kg QW was intravenously administered to cynomolgus monkeys (N = 6 to 10/group) in the 3-week and 13-week repeated-dose toxicity studies to evaluate the effects of belantamab mafodotin on clinical signs. No effects of belantamab mafodotin were noted [see Section 5.2].

Belantamab mafodotin 3, 10, or 30 mg/kg QW was intravenously administered to rats (N = 20 to 32/group) in the 3-week repeated-dose toxicity study and belantamab mafodotin 3, 10, or 30 mg/kg Q3W was intravenously administered to rats (N = 24 to 36/group) in the 13-week repeated-dose toxicity study to evaluate the effects of belantamab mafodotin on clinical signs. No effects of belantamab mafodotin were noted [see Section 5.2].

In a 5-day repeated toxicity study, cys-mcMMAF 0.5, 2, or 5 mg/kg QD was intravenously administered to cynomolgus monkeys (N = 10/group) to evaluate the effects of cys-mcMMAF on respiration rate. No

[15)] A complex composed of MMAF and protease-resistant maleimidocaproyl (mc) linker connected to cysteine residues

effects of cys-mcMMAF were noted [see Section 5.2].

3.R Outline of the review conducted by PMDA

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

3.R.1 Mechanism of action and efficacy of belantamab mafodotin

The applicant's explanation about the mechanism of action of belantamab mafodotin and its efficacy in the treatment of MM:

B-cell maturation antigen is expressed on normal B-lineage cells, and it has been reported that its expression increases when B cells are differentiated into plasma blasts and bone marrow plasma cells, as well as by transformation of plasma cells into malignant cells (*J Immunol*. 2007;179:7276-86, *Immunotherapy*. 2015;7:1187-99).

Belantamab mafodotin is an ADC consisting of belantamab, a humanized anti-BCMA monoclonal antibody, conjugated by a peptide linker to a tubulin polymerization inhibitor, MMAF. Belantamab mafodotin binds to BCMA expressed on the tumor cell membrane [see Section 3.1.1]. Upon internalization into the cell, free cys-mcMMAF is released from the antibody component, which is thought to induce apoptosis [see Section 3.1.4] and other effects, leading to inhibition of tumor growth. In addition, the antibody component of belantamab mafodotin binds to BCMA, inducing ADCC activity and ADCP activity [see Sections 3.1.5 and 3.1.6], which also contributes to the tumor growth inhibition effect of belantamab mafodotin.

In addition to the mechanism of action described above, belantamab mafodotin inhibited tumor growth in xenograft SCID mice bearing subcutaneous human MM cells [see Section 3.1.8.2.1]. Based on this and other factors, belantamab mafodotin is expected to be effective in the treatment of MM.

PMDA accepted the applicant's explanation.

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

The pharmacokinetics (PK) of belantamab mafodotin in animals was studied in rats, monkeys, and other animals. Human or animal biological samples were used to evaluate plasma protein binding, drug metabolizing enzymes, transporters, and other factors of belantamab mafodotin or its component, cys-mcMMAF.

In this section, the term total monoclonal antibody (total mAb) was used to refer to anti-BCMA antibody (belantamab) with or without cys-mcMMAF.

Belantamab mafodotin and total mAb in rat and monkey plasma were determined by immunoassay (lower limit of quantification, for both analytes, 50 or 250 ng/mL in rat plasma, 500 ng/mL in monkey

plasma), while cys-mcMMAF in rat and monkey plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 0.5 or 0.05 ng/mL in rat plasma, 0.15 or 0.05 ng/mL in monkey plasma). Anti-belantamab mafodotin antibodies in rat and monkey plasma were measured by electrochemiluminescence (ECL).

4.1 Absorption

4.1.1 Single-dose studies

A single intravenous dose of belantamab mafodotin 1 mg/kg, or cys-mcMMAF 0.3, 1, or 3 mg/kg was administered to male monkeys, and plasma concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF were evaluated (Table 13). The PK of belantamab mafodotin was similar to that of total mAb. Within the dose range studied, the C_{max} and AUC_{tau} of cys-mcMMAF increased approximately dose proportionally.

Table 13. Pharmacokinetic parameters of belantamab mafodotin, total mAb, and cys-mcMMAF (male monkeys, single intravenous administration)

Administered compound	Analyte	Dose (mg/kg)	C_{max} (μg/mL[*1])	AUC_{tau} (μg·h/mL[*2])	$t_{1/2}$ (h)
Belantamab mafodotin	Belantamab mafodotin	1	29.2 ± 0.694	913 ± 91.3	102 ± 15.1
	Total mAb	1	26.8 ± 0.804	1,040 ± 133	—
cys-mcMMAF	cys-mcMMAF	0.3	1,560 ± 74.8	309 ± 16.1	9.46 ± 3.43
		1	2,820 ± 2,060	621 ± 181	5.42 ± 0.264
		3	14,500 ± 4,390	2,490 ± 752	4.69 ± 0.792

Mean ± standard deviation; —, not calculated; N = 3; *1, ng/mL for cys-mcMMAF; *2, ng·h/mL for cys-mcMMAF

4.1.2 Repeated-dose studies

Intravenous doses of belantamab mafodotin 1, 3, or 10 mg/kg were administered to male and female monkeys QW for 3 weeks or 13 weeks, and plasma concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF were evaluated (Table 14 and Table 15). Within the dose range studied, the C_{max} and AUC_{tau} of belantamab mafodotin, total mAb, and cys-mcMMAF increased approximately dose proportionally.

Anti-belantamab mafodotin antibodies were detected in 24 of 36 animals in the 13-week repeated-dose study.

Table 14. Pharmacokinetic parameters of belantamab mafodotin, total mAb, and cys-mcMMAF (male and female monkeys, repeated-dose intravenous administration for 3 weeks)

Analyte	Dose (mg/kg)	Dosing day (Day)	C_{max} (μg/mL*1)		AUC_{0-167} (μg·h/mL*2)		$t_{1/2}$ (h)	
			Male	Female	Male	Female	Male	Female
Belantamab mafodotin	1	1	22.3 ± 2.54	22.4 ± 3.59	883 ± 176	847 ± 106	—	—
		15	26.7 ± 3.00	28.2 ± 3.65	1,180 ± 236	1,290 ± 79.3	—	—
	3	1	63.5 ± 10.2	54.0 ± 9.87	2,330 ± 198	2,330 ± 448	—	—
		15	66.7 ± 5.11	59.8 ± 19.5	3,590 ± 274	3,920 ± 463	91.2, 135*3	62.3, 132*3
	10	1	251 ± 18.6	247 ± 20.0	11,300 ± 732	11,100 ± 1370	—	—
		15	292 ± 27.0	292 ± 36.3	20,500 ± 804	22,500 ± 849	—	—
Total mAb	1	1	21.9 ± 2.29	20.2 ± 1.47	978 ± 196	917 ± 88.1	—	—
		15	26.3 ± 2.91	28.2 ± 2.56	1,500 ± 210	1,540 ± 146	—	—
	3	1	62.1 ± 8.18	53.3 ± 9.50	2,650 ± 291	2,690 ± 522	—	—
		15	70.5 ± 6.65	65.8 ± 15.2	4,400 ± 510	4,840 ± 427	101, 104*3	61.3, 132*3
	10	1	238 ± 20.9	233 ± 23.0	11,870 ± 1,010	13,300 ± 205	—	—
		15	292 ± 33.0	321 ± 39.4	24,200 ± 1,780	27,500 ± 1,370	—	—
cys-mcMMAF	1	1	0.821 ± 0.0807	0.624 ± 0.336	11.8 ± 3.10	20.0 ± 12.2	—	—
		15	0.422 ± 0.00448	0.576 ± 0.321	12.2 ± 7.73	12.1 ± 4.06	—	—
	3	1	1.57 ± 0.887	2.36 ± 1.47	62.5 ± 19.0	69.5 ± 13.4	—	—
		15	2.26 ± 0.711	1.68 ± 0.721	85.6 ± 15.1	61.5 ± 11.5	—	—
	10	1	4.78 ± 0.873	4.70 ± 1.94	248 ± 70.0	167 ± 11.8	—	—
		15	5.97 ± 1.65	4.83 ± 1.71	416 ± 102	284 ± 7.93	—	—

Mean ± standard deviation (for N = 2, individual values); —, not calculated; N = 3; *1, ng/mL for cys-mcMMAF; *2, ng·h/mL for cys-mcMMAF; *3, N = 2

Table 15. Pharmacokinetic parameters of belantamab mafodotin, total mAb, and cys-mcMMAF*1 (male and female monkeys, repeated-dose intravenous administration for 13 weeks)

Analyte	Dose (mg/kg)	Dosing day (Day)	C_{max} (μg/mL*2)		AUC_{tau} (μg·h/mL*3)	
			Male	Female	Male	Female
Belantamab mafodotin	1	22	25.4, 28.9	26.7 ± 3.18	1,330, 1,380	1,040 ± 232
		85	25.0, 30.4	27.0 ± 1.59	1,180, 1,370	1,030 ± 200
	3	22	81.8 ± 12.4	85.6 ± 5.52	5,200 ± 1,260	5,260 ± 640
		85	94.6 ± 11.4	93.2 ± 11.2	6,570 ± 1,370	6,870 ± 1,440
	10	22	302 ± 41.4	320 ± 14.2	21,600 ± 3,500	21,400 ± 1,700
Total mAb	1	22	25.7, 28.5	26.2 ± 2.02	1,590, 1,680	1,200 ± 333
		85	26.2, 30.1	29.5 ± 2.24	1,640, 1,760	1,370 ± 314
	3	22	88.4 ± 13.8	94.2 ± 6.08	5,960 ± 1,550	6,010 ± 831
		85	103 ± 14.3	104 ± 12.4	8,140 ± 1,850	7,930 ± 1,810
	10	22	380 ± 66.6	356 ± 27.4	30,200 ± 7,470	28,600 ± 2,770
cys-mcMMAF	1	22	0.129 ± 0.0918	0.232 ± 0.0504	5.12 ± 3.62	—
		85	—	0.196 ± 0.0196	—	—
	3	22	0.388 ± 0.0568	0.437 ± 0.100	23.1 ± 8.47	31.2 ± 3.42
		85	0.396 ± 0.0330	0.433 ± 0.0487	25.1 ± 6.84	25.5 ± 5.23

Mean ± standard deviation (for N = 2, individual values); —, not calculated; N = 3; *1, PK parameters for Day 1 were not calculated; *2, ng/mL for cys-mcMMAF; *3, ng·h/mL for cys-mcMMAF

4.2 Distribution

4.2.1 Tissue distribution

A single intravenous dose of 30 mg/kg of belantamab mafodotin with the antibody part fluorescently labeled was administered to female rats, and the tissue distribution of belantamab mafodotin was evaluated. On Day 35, tissue belantamab mafodotin concentrations were 749 ng/g (eyeball) and 462 ng/g (liver). Belantamab mafodotin was not distributed in the cornea.

A single intravenous dose of belantamab mafodotin 30 mg/kg was administered to female rats, and tissue distribution of cys-mcMMAF was evaluated using nano-liquid chromatography-mass spectrometry (nano-LC-MS). At 24 hours and 48 hours post-dose, cys-mcMMAF was detected by the nano-LC-MS method in the liver (968 and 196 ng/g at 24 and 48 hours post-dose, respectively; the same applies hereinafter for the order of timepoint), kidney (40 and 30 ng/g), Harderian gland (15 ng/g for both timepoints), extraorbital lacrimal gland (5 and 4 ng/g), and bone marrow (154 and 137 ng/g). Cys-mcMMAF was not detected in the cornea, eyeball, or eyelids. In the analysis using matrix assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI), cys-mcMMAF was not detected in the eyeball, eyelids, extraorbital lacrimal gland, or liver. In the analysis using secondary ion mass spectrometry (SIMS), cys-mcMMAF was not detected in the eyeball or eyelids.

Intravenous doses of belantamab mafodotin 15 or 30 mg/kg were administered to female rabbits QW for 2 or 4 weeks, and the distribution of belantamab mafodotin, etc. in lacrimal fluid was evaluated. Belantamab mafodotin, total mAb, and cys-mcMMAF were detected in 91 of 126 specimens, 64 of 126 specimens, and 76 of 81 specimens, respectively.

Intravenous doses of belantamab mafodotin 30 mg/kg were administered QW for 4 weeks to female rabbits, followed by belantamab mafodotin 15 mg/kg QW intravenously for 3 weeks, and the distribution of belantamab mafodotin, etc. in tear fluid and plasma was evaluated. The plasma to tear fluid belantamab mafodotin concentration ratio ranged from 45.6 to 199, indicating that the belantamab mafodotin concentration was higher in plasma than in tear fluid. The belantamab mafodotin to cys-mcMMAF molar ratio was 1,410 to 1,940 in plasma and 26.0 to 80.0 in tear fluid, indicating that the belantamab mafodotin molar concentration was higher than the cys-mcMMAF molar concentration in both plasma and tear fluid.

4.2.2 Plasma protein binding

After incubating cys-mcMMAF (0.001 to 1 μmol/L) in plasma from mice, rats, monkeys, or humans at 37°C for 5 hours, plasma protein binding of cys-mcMMAF was evaluated by equilibrium dialysis. Unbound fractions of plasma proteins of cys-mcMMAF were 65% to 68% (mouse), 33% to 36% (rat), 88% to 89% (monkey), and 84% to 86% (human).

4.2.3 Placental to fetal transfer

No studies were conducted to investigate placental transfer or maternal-fetal transfer of belantamab mafodotin. Given that human IgG can cross the placenta to the fetus, the applicant stated that since belantamab mafodotin has the structure of humanized IgG1 monoclonal antibody, it can also cross the placenta to the fetus.

4.3 Metabolism

4.3.1 Stability in plasma

Belantamab mafodotin (100 μg/mL) was incubated with rat, monkey, or human plasma at 37°C for 96 hours, and the plasma stability of belantamab mafodotin was evaluated. The percentage of free cys-mcMMAF released from belantamab mafodotin was 0.24%, 1.48%, and 3.08% in rat, monkey, and human plasma, respectively.

The applicant explained that the results showed that the release of free cys-mcMMAF from belantamab mafodotin in plasma is limited, suggesting that belantamab mafodotin remains stable in plasma.

4.3.2 *In vitro*

The metabolites of cys-mcMMAF were investigated using recombinant human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), flavin-containing monooxygenase (FMO), mouse, rat, monkey, and human hepatocytes. The recombinant enzyme samples (CYPs and FMO) were incubated with ^{3}H-labeled cys-mcMMAF 1 μmol/L for 1 hour in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), while the hepatocyte samples were incubated with ^{3}H-labeled cys-mcMMAF 10 μmol/L for 4 hours. In all the above evaluations, neither oxidative nor conjugated metabolites were detected, and hydrolysis products and isomers, which are non-enzymatic reaction metabolites, were detected.

The metabolites of cys-mcMMAF were investigated by incubating rat, monkey, or human liver S9 fractions with ^{3}H-labeled cys-mcMMAF 10 μmol/L in the presence or absence of NADPH and uridine diphosphate glucuronic acid (UDPGA) for 120 minutes. It was found that in the presence of NADPH and UDPGA, isomers were mainly detected as non-enzymatic reaction metabolites, similarly to those observed in the absence of NADPH and UDPGA.

The applicant explained that the above results suggest that non-enzymatic reactions are primarily involved in the metabolism of cys-mcMMAF.

4.3.3 *In vivo*

A single intravenous dose of ^{3}H-labeled cys-mcMMAF 10 mg/kg was administered to male rats to evaluate metabolites in urine and feces. Mainly unchanged cys-mcMMAF was detected in urine collected up to 24 hours post-dose, accounting for 9.3% of the radioactivity administered. Mainly cys-mcMMAF isomers were detected in feces collected up to 48 hours post-dose, accounting for 13.8% of the radioactivity administered.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

Intravenous doses of belantamab mafodotin 3, 10, or 30 mg/kg were administered to male and female rats QW for 3 weeks to evaluate cys-mcMMAF in urine. The total amount of cys-mcMMAF collected in urine increased dose proportionally.

A single intravenous dose of ^{3}H-labeled cys-mcMMAF 10 mg/kg was administered to male rats to evaluate the radioactivity excreted in urine and feces (percentage of the radioactivity administered). It was found that12.5% (urine) and 82.7% (feces) of the radioactivity administered was detected up to 48 hours post-dose.

Based on the results of the *in vivo* metabolism study results [see Section 4.3.3] in addition to the above, the applicant explained that cys-mcMMAF is mainly metabolized as an isomer and excreted in feces.

4.4.2 Excretion into breast milk

Whether belantamab mafodotin is excreted into breast milk has not been studied.

The applicant explained that since human IgG is excreted into breast milk, it is likely that belantamab mafodotin, which contains an IgG1 subclass humanized antibody, is also excreted into breast milk.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

Given the following evaluation results, it is unlikely that the pharmacokinetic drug interactions via the inhibition of CYP isoforms by cys-mcMMAF will occur in clinical use.

- Human liver microsomes and cys-mcMMAF (0.001 to 1 μmol/L) were incubated with the substrates[16)] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A in the presence or absence of NADPH to investigate inhibition of CYP isoforms by cys-mcMMAF. For all CYP substrates studied, cys-mcMMAF did not exhibit a clear inhibitory effect on metabolism.
- Human liver microsomes and cys-mcMMAF (0.001 to 1 μmol/L) were pre-incubated in the presence or absence of NADPH, followed by incubation with substrates[16)] for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A to investigate the time-dependent inhibition of the CYP isoforms by cys-mcMMAF. For all CYP substrates studied, cys-mcMMAF did not exhibit a clear time-dependent inhibitory effect on metabolism.

4.5.2 Enzyme induction

The applicant's explanation:

16) The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), efavirenz (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), S-mephenytoin (CYP2C19), dextromethorphan (CYP2D6); testosterone and midazolam as substrates for CYP3A.

Given the following evaluation results, it is unlikely that the pharmacokinetic drug interactions via the induction of CYP isoforms by cys-mcMMAF will occur in clinical use.

- Human hepatocytes were incubated with cys-mcMMAF (10, 100, or 1,000 nmol/L) for 72 hours, and messenger ribonucleic acid (mRNA) expression of CYP1A2, CYP2B6, and CYP3A and enzyme activity of these CYP isoforms were evaluated. There were no increases in the mRNA expression or enzyme activity by cys-mcMMAF in any of the CYP isoforms.

4.5.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic drug interactions of cys-mcMMAF:

The evaluation results on transporter substrates outlined below suggest that cys-mcMMAF is a substrate of organic anion transporting polypeptide (OATP)1B1, OATP1B3, multidrug resistance-associated proteins (MRP)1, MRP2, MRP3, and P-glycoprotein (P-gp). However, given the low levels of free cys-mcMMAF in plasma released from belantamab mafodotin [see Section 4.3.1] and low plasma concentrations of cys-mcMMAF in clinical use [see Sections 6.2.2.2 and 6.2.2.3], it is unlikely that pharmacokinetic drug interactions will pose a problem when belantamab mafodotin is administered in combination with the inhibitors of the above transporters in clinical use.

- Using Madin-Darby canine kidney type II (MDCK II) expressing human P-gp, transport of cys-mcMMAF (100 nmol/L) mediated by P-gp was evaluated. The efflux ratio of cys-mcMMAF in the presence and absence of P-gp inhibitor (verapamil, 60 μmol/L) was 1.1 and 34, respectively.
- Using MDCK II cells expressing human BCRP, transport of ^{3}H-labeled cys-mcMMAF (0.72, 7.2, or 14.4 nmol/L) mediated by BCRP was evaluated. The efflux ratio of cys-mcMMAF was <2 at all concentrations studied.
- Using membrane vesicles prepared from the HEK293 cells expressing the human bile salt export pump (BSEP), MRP2, MRP3, MRP4, or MRP5, transport of ^{3}H-labeled cys-mcMMAF (14.4 nmol/L) mediated by the above transporters was evaluated. The results showed that in the membrane vesicles expressing MRP2, MRP3, and BSEP, the cys-mcMMAF uptake ratio (presence-to-absence of ATP) was 13.5, 4.21, and 1.89, respectively. In the presence of the inhibitor[17)] for each transporter, these ratios were decreased to 0.9, 1.18, and 0.95, respectively. Conversely, in membrane vesicles expressing MRP4 and MRP5, the cys-mcMMAF uptake ratios (presence-to-absence of ATP) were 1.10 and 1.20, respectively.
- Using membrane vesicles prepared from insect ovarian tissue Sf9 cells expressing human MRP1, transport of ^{3}H-labeled cys-mcMMAF (14.4 nmol/L) mediated by MRP1 was evaluated. The results showed that the cys-mcMMAF uptake ratio (presence-to-absence of ATP) was 11.17, and in the presence of MRP1 inhibitor (MK571, 150 μmol/L), the uptake ratio was decreased to 0.82.

[17)] The following compounds were used as inhibitors for the transporters: ciclosporin A 10 μmol/L (BSEP), benzbromarone 200 μmol/L (MRP2), sulfasalazine 1,000 μmol/L (MRP3), MK571 150 μmol/L (MRP4), and benzbromarone 150 μmol/L (MRP5).

- Using MDCK II or HEK293 cells expressing human OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion (MATE)1, or MATE2-K, transport of ^{3}H-labeled cys-mcMMAF (14.4 nmol/L) mediated by the above transporters was evaluated. The results showed that uptake of cys-mcMMAF was not observed in the cells expressing OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K. The results showed that the cys-mcMMAF uptake ratios (OATP1B1-expressing cells to non-expressing cells, OATP1B3-expressing cells to non-expressing cells) were 13.28 and 4.94, respectively, and in the presence of rifampicin 50 μmol/L (inhibitor of OATP1B1 and OATP1B3), the uptake ratios were decreased to 0.93 and 0.82, respectively.

Given the following evaluation results on the inhibition of transporters, it is unlikely that the pharmacokinetic drug interactions via the inhibition of transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MRP1, MRP2, MRP3, MRP4, MRP5, BCRP, BSEP, MATE1, MATE2-K, and P-gp) by cys-mcMMAF will occur in clinical use.

- Using HEK293 cells expressing human P-gp, BCRP, BSEP, MRP2, MRP3, MRP4, or MRP5, and membrane vesicles prepared from insect ovarian tissue Sf9 cells expressing human MRP1, inhibition of transport of the transporter substrates[18)] by cys-mcMMAF (20 or 200 nmol/L) was evaluated. It was found that cys-mcMMAF had no clear inhibitory effect on the transport of substrates for P-gp, BCRP, BSEP, MRP1, MRP3, MRP4, and MRP5. While uptake of MRP2 substrate by cys-mcMMAF increased by 54%, no clear inhibitory effect on the transport of the MRP2 substrate was observed.
- Using MDCK II cells or HEK293 cells expressing human OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K, inhibition of transport of the transporter substrates[19)] by cys-mcMMAF (20 or 200 nmol/L) was evaluated. It was found that cys-mcMMAF did not have a clear inhibitory effect on the transport of any substrate for these transporters.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of belantamab mafodotin is acceptable.

5. Toxicology and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in rats and cynomolgus monkeys to evaluate the acute toxicity of belantamab mafodotin via the intravenous route (Table 16). In the rat study, because deaths were observed at a belantamab mafodotin dose of 100 mg/kg, the approximate lethal dose was

18) The following compounds were used as substrates for the transporters: N-methyl-quinidine 1 μmol/L (P-gp), estrone-3-sulfate 1 μmol/L (BCRP), taurocholic acid 0.2 μmol/L (BSEP), leukotriene C_4 50 nmol/L (MRP1), estradiol-17β-glucuronide 100 μmol/L (MRP2), estradiol-17β-glucuronide 10 μmol/L (MRP3), dehydroepiandrosterone sulfate 0.5 μmol/L (MRP4), and 5(6)-carboxy-2',7'-dichlorofluorescein 5 μmol/L (MRP5).

19) The following compounds were used as substrates for the transporters: estradiol-17β-glucuronide 1 μmol/L (OATP1B1), cholecystokinin-8, 0.1 μmol/L (OATP1B3), p-aminohippuric acid 5 μmol/L (OAT1), and estrone-3-sulfate 1 μmol/L (OAT3); metformin 10 μmol/L as substrates for OCT1, OCT2, MATE1, and MATE2-K.

determined to be 100 mg/kg. In the cynomolgus monkey study, because no deaths were reported at a belantamab mafodotin dose of up to 30 mg/kg, the approximate lethal dose was determined to be >30 mg/kg. Acute symptoms in rats after single dose administration included unsteady gait, swollen hindlimbs, and hyperreactivity to sound. In cynomolgus monkeys, vomiting and abnormal feces were observed.

Table 16. Single-dose toxicity studies

Test system	Route	Dose (mg/kg)	Major findings	Approximate lethal dose (mg/kg)	CTD
Male/ female rats	IV	0,* 10, 30, 100	Unscheduled deaths: At 100, 2/8 (females) Swollen/limited movement of hindlimbs, unsteady gait, decrease in movement, emaciated flanks, piloerection, wounds/scabs/contusions over whole body, labored breathing, hyperreactivity to sound Animals that survived: At ≥10, inflammatory cell infiltration at the injection site At ≥30, injection site epidermal hyperplasia/skeletal muscle degeneration/necrosis/scabs At 100, swollen hindlimbs, piloerection, skin reddening on the tail, raised area on the skin in the lumbar region, thinning fur in the abdomen, low weight gain	100	4.2.3.1-2 (reference data)
Male/ female cynomolgus monkeys	IV	0,* 3, 10, 30	At ≥3, decreased appetite, low body weight, abnormal feces, subcutaneous purpura/reddening/subcutaneous haemorrhage/inflammation at the injection site, fading skin color At 30, vomiting, high CRP levels	>30	4.2.3.1-1 (reference data)

*, Phosphate buffer saline solution

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of belantamab mafodotin, cys-mcMMAF, and belantamab were conducted in rats and cynomolgus monkeys (Table 17 and Table 18).

Findings that are common in belantamab mafodotin-treated rats and cynomolgus monkeys included release of cytokines, decreased red blood cell parameters, increased white blood cell parameters, kidney tubular degeneration/regeneration and associated urinary renal marker abnormalities, macrophage infiltrates and increased mitotic figures in multiple organs, inflammatory change, hepatic enzyme abnormalities, and seminiferous tubule degeneration/atrophy. Findings unique to rats were corneal opacities/single cell necrosis, increased alveolar macrophages, eosinophilic materials in alveoli, luteinized nonovulatory follicles, degeneration of the incisor ameloblast/odontoblast layers, while those unique to cynomolgus monkeys were hemorrhage/encapsulated hematoma in the inguinal region, and hepatocellular necrosis. The applicant considered that these findings were either caused by the cytotoxic effects of cys-mcMMAF or a systemic inflammatory response to belantamab mafodotin.

In the 13-week repeated dose toxicity studies in rats and cynomolgus monkeys, toxicity findings were noted at the lowest dose level of belantamab mafodotin. The blood exposure (AUC_{tau}) of belantamab

mafodotin at the lowest dose (integrated male/female mean) for rats and cynomolgus monkeys was 10,500 μg·h/mL and 1,130 μg·h/mL, respectively, approximately corresponding to 1.9-fold and 0.2-fold the clinical exposure.[20)]

In rats and cynomolgus monkeys treated with cys-mcMMAF, mild and transient laboratory parameter changes, as well as findings in the eye and the lung, were observed. The applicant explained that the limited toxicological findings for cys-mcMMAF compared with those for belantamab mafodotin reflected the lower cell membrane permeability of cys-mcMMAF due to its charged C-terminal phenylalanine residue (*Bioconjug Chem.* 2006;17:114-24).

In cynomolgus monkeys subjected to early euthanasia following administration of belantamab mafodotin, anti-drug antibody (ADA) production, and granular deposits containing IgG and/or IgM in the renal glomerulus, the blood vessel walls in the gastrointestinal tract, and in the Kupffer cells in the liver were noted. This may suggest that worsening of clinical signs in this animal is attributable to severe renal toxicity caused by immune complex deposition. However, antibody production observed in animals after administration of belantamab mafodotin, which contains a humanized antibody, has not been proven to predict antibody production in humans (*Reg Tox Pharmacol.* 2017;88:125-37). The applicant explained that these events are therefore not likely to be extrapolatable to humans.

Degeneration of the incisor ameloblast/odontoblast layers noted in rats treated with belantamab mafodotin is a known toxicity in rodents after administration of an agent such as a microtubule polymerase inhibitor, which targets rapidly dividing cells (*Acta Pathol Microbiol Scand A.* 1977;85:319-29, *Toxicol Pathol.* 2001;29:292-9). However, given that unlike rodents, in humans, incisors will not continue to grow throughout life, and that similar findings have not been noted for cynomolgus monkey or rat molars, the applicant explained that these events are not likely to be extrapolatable to humans.

Adverse events similar to the effects of belantamab mafodotin on the kidney and liver noted in the above studies also occurred in clinical studies in some participants. However, the applicant explained that based on the incidence and degree of severity, the safety risk is acceptable in clinical use.

Regarding toxicity findings in red blood cell parameters, white blood cell parameters, and in the lungs following administration of belantamab mafodotin, the need for cautionary statements based on the incidence of adverse events in the clinical studies (ant other factors) will be discussed in Sections "7.R.3.3 Blood cell reduction" and "7.R.3.7 IDL."

Table 17. Repeated-dose toxicity studies in rats

Test system	Route	Dosing period	Dose (mg/kg/dose)	Major findings[*3]	NOAEL (mg/kg)	CTD

[20)] Belantamab mafodotin exposure in blood (AUC_{tau}) 5,490 μg·h/mL following administration of 3 intravenous doses of belantamab mafodotin 2.5 mg Q3W to Japanese patients with relapsed or refractory MM in a global phase III study (DREAMM-3 study)

Male/ female rats	IV	3 weeks (QW) + 12-week recovery period	Belantamab mafodotin 0,[*1] 3, 10, 30	Unscheduled deaths: At 30, 1/10[*4] (female) Reddening of mandibular lymph nodes, alveolar eosinophilic materials, increased alveolar macrophages, corneal single cell necrosis, injection site hemorrhage, congestion of multiple tissues Animals that survived: At ≥3, increased blood ALT/albumin/total protein/calcium/lipocalin/α1-acid glycoprotein/α2-macroglobulin, increased MCP-1, increased TNF-α, increased urine lipocalin-2/RPA-1, corneal single cell necrosis, perivascular inflammation at injection sites, increased alveolar macrophages, alveolar eosinophilic materials, extramedullary hematopoiesis in the spleen At ≥10, decreased hematocrit/hemoglobin/MCH/MCV, increased RDW/platelet count, increased blood GDH/AST/ALP/cholesterol/aldolase/creatine kinase, increased IL-6, increased urine total protein/KIM-1, extramedullary hematopoiesis in the liver, luteinized nonovulatory follicles, in the spleen, congestion/lymphocytolysis/pigmented macrophages, bone remodeling in the sternum, seminiferous tubule degeneration/atrophy, decreased weight of testes/thymus, testicular softening, localized hyperplasia of epidermis at the injection site, inflammatory cell infiltrate of mixed cells in the epididymides At 30, decreased body weight gain, decreased food consumption, decreased red blood cell count/white blood cell count/neutrophil count/lymphocyte count/monocyte count/eosinophil count/basophil count, increased blood urea, decreased blood total bilirubin/blood triglycerides, increased IL-1β, increased urine albumin/αGST, increased liver weight, enlarged spleen, increased spleen weight, reduced size of epididymis/thymus, epididymis aspermia/hypospermia, focal skeletal muscle degeneration/necrosis at the injection site, femur bone remodeling, kidney tubular degeneration, multinucleate giant cells in the lymph nodes, epithelial single cell necrosis of the mammary gland, decreased cellularity/single cell necrosis of bone marrow in the sternum, thymus decreased cellularity/mixed cell inflammatory cell infiltrate/lymphocytolysis Recovery period At 30, maxillary incisor ameloblast layer degeneration/pale or white discoloration/abnormal wearing/longer/thicker, increased liver weight, increased blood cholesterol, testicular softening/epididymides, seminiferous tubule atrophy, epididymis aspermia, pale lung, alveolar macrophages aggregate	3	4.2.3.2-3
		13 weeks (Q3W) + 12-week recovery period	Belantamab mafodotin 0,[*1] 3, 10, 30	At ≥3, decreased MCV/MCH, increased white blood cell count, pale areas in the lung, testis discoloration/reduced size/softening, seminiferous tubule degeneration/atrophy, epididymis reduced size/aspermia, increased alveolar macrophages, alveolar eosinophilic materials, increased mitotic figures in the cornea, increased vacuolation in the pars distalis of the pituitary gland At ≥10, decreased body weight gain, increased neutrophil count/reticulocyte count/lymphocyte count/RDW, decreased hematocrit, decreased myeloid cells, increased erythroid lineage cells, decreased M:E ratio, increased fibrinogen, increased KC/GRO, decreased testis weight, epididymis dark areas/softening, congestion in the spleen,	<3	4.2.3.2-6

				corneal single cell necrosis, incisor degeneration (ameloblast and odontoblast degeneration), atrophy of the lobules in the mammary gland At 30, decreased hemoglobin concentration, increased monocyte count/large unstained cell count, increased AST/ALT, increased blood total protein/albumin/calcium, decreased blood triglycerides, increased urine albumin/total protein/KIM-1, increased TNF-α, increased spleen/liver weight, enlarged spleen, testis dark areas/pale areas, kidney tubular degeneration/regeneration, extramedullary hematopoiesis in the liver Recovery period At ≥10, lung pale areas/perivascular inflammatory cell infiltrate, increased alveolar macrophages, decreased weight/discoloration/reduced size/softening of the testis, epididymis aspermia/hypospermia, increased vacuolation in the pars distalis of the pituitary gland At 30, increased urine albumin, reduced size of epididymis, alveolar eosinophilic materials		
		5 days (QD) + 2-week recovery period	cys-mcMMAF 0,[*2] 1, 5, 10	At ≥1, alveolar histiocytosis At ≥5, black/brown/red materials around the eyes/snout, corneal opacity, increased lung weight, lung subacute inflammation At 10, increased neutrophil count, increased RDW, increased AST/ALT <u>Recovery period</u> At ≥5, alveolar histiocytosis	10	4.2.3.2-4

*1, A 25 mmol/L aqueous citrate buffer containing 0.05 mmol/L EDTA, 200 mmol/L trehalose, and 0.02% polysorbate 80; *2, phosphate buffer saline; *3, Because the findings were mild in severity or without associated histopathological observations, it was determined that findings reported at lower than the no-observed adverse effect level (NOAEL) were of low toxicological significance; *4, It was determined that the death was not belantamab mafodotin-related because the animal died prior to dosing in a restraint tube, there were no abnormalities in clinical signs, and no abnormal findings were noted compared to animals that survived.

Table 18. Repeated-dose toxicity studies in cynomolgus monkeys

Test system	Route	Dosing period	Dose (mg/kg/dose)	Major findings[*5]	NOAEL (mg/kg)	CTD
Male/ female cynomolgus monkeys	IV	3 weeks (QW) + 12-week recovery period	Belantamab mafodotin 0,[*2] 1, 3, 10	At ≥1, decreased body weight, decreased blood IgM At ≥3, decreased blood albumin, increased CRP, decreased NK cell count, increased macrophages in red pulp of the spleen, increased mitoses in Kupffer cells in the liver sinusoid, increased thymus cortex macrophages At 10, reduced appetite, increased white blood cell count/neutrophil count/monocyte count/large unstained cell count, decreased hemoglobin/red blood cell count/hematocrit, increased RDW/reticulocyte count, increased nucleated red blood cells/Howell-Jolly bodies, decreased platelet count, increased macrophages in the bone marrow, APTT prolongation, increased blood AST/ALT/GDH/GGT/total bilirubin/total cholesterol/triglycerides, decreased blood IgG, increased urine albumin/total protein, increased activated B cell count, decreased thymus weight, decreased thymic cortex cellularity, increased liver weight, increased mitoses in the glomerular mesangium cells/histiocytes in the cortex of the kidney, kidney glomerulopathy, distal nephron degeneration/regeneration Recovery period At 3, decreased blood IgM	1	4.2.3.2-2
		13 weeks (QW) + 12-week recovery period [*1]	Belantamab mafodotin 0,[*2] 1, 3, 10	<u>Sacrificed moribund</u> At 10, 1/3 (male) decrease in movement, weakening, decreased muscle tone, hunchback position, abdominal distension, pale skin, partial eyelid closure, reduced appetite, liquid stool, salivation, clear discharge around the nose area, dehydration, decreased body temperature, kidney tubular degeneration/regeneration, glomerulonephritis, gastrointestinal tract hemorrhage, mesenteric lymph node hemorrhage, lung/gastrointestinal tract hemorrhage/thrombus/fibrinoid vascular necrosis, fluid accumulation in the abdominal cavity, thymic vascular necrosis, heart/adrenal gland hemorrhage, ADA production, deposition of granules containing cytoplasmic IgG/IgM (glomerular tufts in the kidney/tunica media of blood vessels in the gastrointestinal tract/Kupffer cells in the liver/sinusoidal lining cells in the liver), seminiferous tubule degeneration <u>Animals that survived</u> At ≥1, ADA/circulating immune complex (CIC) production, increased MCP-1 At ≥3, mass/skeletal muscle hemorrhages/encapsulated hematomas in the inguinal region, increased fibrinogen, increased blood AST/ALT/ALP, increased urine albumin/total protein, decreased blood IgM, in bone marrow, increased M:E ratio, increased activated macrophages/a left shift in the maturation sequence of the erythroid cell line, increased metarubricytes, decreased NK count, reduced size/decreased weight of the thymus, decreased lymphocyte cellularity in the thymus, urothelial single cell necrosis in the kidney/urinary bladder, sciatic nerve hemorrhage, increased macrophages in the choroid plexus in the brain, dark focus in the liver, multifocal hepatocellular necrosis, liver Kupffer cell hypertrophy/hyperplasia/increased mitotic figures, increased macrophages/increased mitotic figures/decreased	1	4.2.3.2-7

				lymphocyte cellularity in the spleen, increased mitotic figures in medulla/extramedullary hematopoiesis in the mandibular/mesenteric/inguinal lymph nodes At 10, decreased muscle tone/activity, cold sensation, tremor, hunchback position, emaciation/prominent backbone noted, pale skin/signs of dehydration, reduced appetite, increased neutrophil count/monocyte count/large unstained cell count, increased reticulocyte count, decreased platelet count/hemoglobin, APTT prolongation, increased blood GGT/GDH/cholesterol, decreased blood albumin, increased blood direct/indirect bilirubin, increased CRP, increased kidney weight, pale/dark areas in the kidney, kidney tubular degeneration/regeneration, membranoproliferative glomerulonephritis, seminiferous tubule degeneration, decreased lymphoid cellularity in gastrointestinal tract/mesenteric lymph nodes, spleen lymphoid necrosis <u>Recovery period</u> At 3, decreased NK cells, decreased bone marrow M:E ratio At 10, intestinal tract submucosal artery/periarterial chronic inflammation, increased metarubricytes, increased mitotic figures, red blood cell morphological anomalies (schistocytes, spherocytes, anisocytosis, polychromasia), increased direct/indirect bilirubin		
		5 days (QD) + 2-week recovery	cys-mcMMAF 0,[*3] 0.5, 2, 5	At ≥0.5, increased lymphocyte count/monocyte count At ≥2, increased large unstained cell count At 5, decreased red blood cell count/hemoglobin/hematocrit/reticulocyte count, increased creatin kinase	5	4.2.3.2-5
	IV or SC	13 weeks (QW)	belantamab IV: 0,[*4] 40 SC: 0,[*4] 2, 10	**Intravenous** At 40, decreased neutrophil count, increased fibrinogen, increased CRP, decreased blood albumin, increased blood IgG, decreased blood IgM, ADA production **Subcutaneous** At ≥2, macrophage vacuolation/perivascular mononuclear cell infiltration at injection sites, decreased neutrophil count, increased blood IgG, decreased blood IgM, ADA production At 10, increased monocyte count, increased fibrinogen, increased CRP, decreased blood albumin	IV: 40 SC: 10	4.2.3.2-10

*1, There was a deterioration in the clinical condition of all animals in the 10 mg/kg group that necessitated termination of dosing at Week 5 and early euthanasia at Week 7, except for the recovery group, for which dosing was stopped at Week 6; *2, a 25 mmol/L aqueous citrate buffer containing 0.05 mmol/L EDTA, 200 mmol/L trehalose, and 0.02% polysorbate 80; *3, phosphate buffer saline; *4, 50 mmol/L sodium acetate trihydrate, 0.05 mmol/L EDTA, 1%L-arginine, 51 mmol/L sodium chloride, and 0.02% polysorbate in water for injection; *5, Because the findings were mild in severity and without associated histopathological observations, it was determined that findings reported at lower than the NOAEL were of low toxicological significance

5.3 Genotoxicity

A bacterial reverse mutation assay (Ames), a gene mutation study using mouse lymphoma cells, and a bone marrow micronucleus assay in rats were performed to evaluate the genotoxicity of cys-mcMMAF. A micronucleus assay using human peripheral blood lymphocytes was performed to evaluate the genotoxicity of belantamab mafodotin (Table 19).

Induction of micronuclei was observed in the micronucleus assay of belantamab mafodotin using human peripheral blood lymphocytes, while the results of all studies showed that cys-mcMMAF was not genotoxic. The applicant explained that the negative results of cys-mcMMAF may be due to the low

cell membrane permeability of cys-mcMMAF due to its charged C-terminal phenylalanine residue. It is considered that the genotoxicity of belantamab mafodotin occurs through an aneugenic mechanism based on the following:

- Monomethyl auristatin E (MMAE) is also a microtubule polymerase inhibitor, which is structurally similar to MMAF. In a bacterial reverse mutation assay and a mutation assay using L5178Y*Tk*$^{+/-}$ mouse lymphoma cells, the results showed that MMAE was not mutagenic; however, in the rat bone marrow micronucleus assay, formation of micronuclei was induced through an aneugenic mechanism (*Mol Cancer Ther*. 2024;23:1483–93).
- In the *in vitro* micronucleus assay of belantamab mafodotin, positive results were obtained.

Table 19. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (µg/plate or µg/mL) dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *E. Coli*: WP2 *uvrA*	S9−	cys-mcMMAF 0,*1 50, 150, 500, 1,500, 5,000	Negative	4.2.3.3.1-1
			S9+	cys-mcMMAF 0,*1 50, 150, 500, 1,500, 5,000		
	Gene mutation study using mouse lymphoma cells	Mouse lymphoma L5178Y*Tk*$^{+/-}$	S9+ (4 hours)	cys-mcMMAF 0,*1 4, 5.34, 7.12, 9.49, 12.7, 16.9, 22.5, 30	Negative	4.2.3.3.1-2
			S9− (4 hours)	cys-mcMMAF 0,*1 4, 5.34, 7.12, 9.49, 12.7, 16.9, 22.5, 30		
			S9− (24 hours)	cys-mcMMAF 0,*1 0.119, 0.238, 0.475, 0.95, 1.27, 1.69, 2.25, 3, 4, 5.34, 7.12		
	Micronucleus assay using human peripheral blood lymphocytes	Human peripheral blood lymphocytes	S9− (24 hours)	Belantamab mafodotin 0,*2 577	Positive	4.2.3.3.1-3 (reference data)
			S9− (24 hours + 24 hours for recovery)	Belantamab mafodotin 0,*2 577		
In vivo	Rat micronucleus assay	Male rat (Sprague Dawley) bone marrow		cys-mcMMAF 0,*3 10, 17.5, 25 (single dose, IV)	Negative	4.2.3.3.2-1

*1, DMSO; *2, a 25 mmol/L aqueous citrate buffer containing 0.05 mmol/L EDTA, 200 mmol/L trehalose, and 0.02% polysorbate 80; *3, phosphate buffer saline

5.4 Carcinogenicity

No carcinogenicity studies were conducted because belantamab mafodotin is an anti-neoplastic agent intended to be used for the treatment of patients with advanced cancer.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted because belantamab mafodotin is an anti-neoplastic agent intended to be used for the treatment of patients with advanced cancer, and it is expected that it would have adverse effects on embryo-fetal development due to the mechanism of targeting rapidly dividing cells.

The effects of belantamab mafodotin on male and female fertility were evaluated in the repeated-dose toxicity studies in rats and cynomolgus monkeys. Testicular toxicity was noted in rats and ovarian toxicity was noted in cynomolgus monkeys [see Section 5.2]. The applicant explained that the above results suggest that belantamab mafodotin may have effects on male and female fertility, and these findings will be included appropriately in the package insert.

The applicant's explanation about the effects of belantamab mafodotin on embryo-fetal development:
Belantamab mafodotin may have adverse effects on embryo-fetal development based on the following:

- Because cys-mcMMAF inhibits microtubule polymerization by targeting rapidly dividing cells [see Section 5.2], belantamab mafodotin may have adverse effects on embryo-fetal development.
- BCMA expression has been reported in the human term placenta during late pregnancy (*Am J Pathol.* 2008;172:1303-11), suggesting that there is a risk that belantamab mafodotin may be specifically transported from the mother to the fetus via BCMA during pregnancy.
- Brentuximab vedotin (genetical recombination), an ADC consisting of an anti-CD30 antibody conjugated to MMAE, has been shown to cross the placenta in rats, causing embryo-fetal toxicities including early resorption, post-implantation deaths, decline in fetal viability, and external abnormalities of the fetus (Review Report of Adcetris for Intravenous Drip Infusion 50 mg, dated November 8, 2013).

In addition to effects on embryo-fetal development, belantamab mafodotin can induce chromosomal aberration [see Section 5.3]; therefore, the following cautionary statements will be included in the package insert:

- Belantamab mafodotin should only be used in women who are or may be pregnant if the treatment benefits outweigh the risks.
- Patients should be instructed to comply with the following directions: women of reproductive potential should use effective contraception during belantamab mafodotin treatment and for 4 months following the last dose. Men with female partners of reproductive potential should use effective contraception during belantamab mafodotin treatment and for 6 months following the last dose.[21)]

5.6 Other toxicity studies

5.6.1 Local tolerance

Local tolerance of belantamab mafodotin by the intravenous route was evaluated in single- or repeated-dose toxicity studies in rats or cynomolgus monkeys [see Sections 5.1 and 5.2]. In the single-dose toxicity studies, perivascular hemorrhage and subcutaneous inflammation at injection sites were noted

21) In accordance with the "Guidance on the Need for Contraception Related to Use of Pharmaceuticals" (PSEHB/PED Notification No. 0216-1, dated February 16, 2023), the proposed duration was selected taking into account an elimination half-life of 14.3 days (*CPT Pharmacometrics Syst Pharmacol.* 2021;10:851-63), estimated for belantamab mafodotin in humans in PPK analyses based on the data from the DREAMM-2 study, a foreign phase IIb study in patients with relapsed or refractory MM.

following single intravenous dose administration of belantamab mafodotin at 2 mg/mL (10 mg/kg group) to rats, which is comparable to the concentration of solution for humans (0.2-2 mg/mL), or at 16.1 mg/mL (3 mg/kg group) to cynomolgus monkeys, which is approximately 8 times the concentration of solution for humans [see Section 5.1].

While belantamab mafodotin at higher concentrations may cause local irritation, in the 13-week repeated-dose toxicity studies in rats or cynomolgus monkeys, no injection site findings indicative of local irritancy were noted following intravenous administration of belantamab mafodotin at doses higher than the concentration of solution for humans (at 3 mg/mL [30 mg/kg group] Q3W to rats, or at 2.5 mg/mL [10 mg/kg group] QW to cynomolgus monkeys) [see Section 5.2]. The applicant explained that it is unlikely that local irritancy-related problems will occur in clinical use of belantamab mafodotin.

5.6.2 Tissue cross-reactivity

Tissue cross-reactivity studies were conducted using normal tissue from humans and cynomolgus monkeys. Positive staining, mainly cytoplasmic, was observed in multiple human tissues examined (Table 20). The applicant considered that staining of cytoplasm, which cannot be normally reached by antibodies *in vivo*, is non-specific, and is of low biological significance.

Table 20. Tissue cross-reactivity studies

Test system	Method	Results	CTD
Human and cynomolgus monkey normal tissue	Human or cynomolgus monkey cryo-sections were incubated with biotinylated belantamab mafodotin or belantamab (1 or 10 µg/mL) and tissue binding was evaluated	Positive staining was observed in the following tissues **Human tissues** (cytoplasm) Adrenal, heart, kidney, liver, lymph node, spleen, tonsil, adipose tissue, skin **Cynomolgus monkeys** (cytoplasm) Adrenal, heart, colon, kidney, liver, lymph node, spleen, tonsil	4.2.3.7.7-1 (reference data)
Normal human tissue	Human cryo-sections were incubated with belantamab mafodotin (2.5, 5, or 10 µg/mL) and tissue binding was evaluated	Positive staining was observed in the following tissues **Cell membrane and cytoplasm** Lung (multifocal, perivascular tissue) **Cytoplasm** Adrenal, cerebellum (blood vessel/capillary vessel walls, scattered white matter cells), cerebral cortex (blood vessel/capillary vessel walls), vascular endothelium, heart (perivascular tissue), lung (alveolar septum), ovary (stroma), fallopian tube, parathyroid gland, peripheral nerve, pituitary gland, placenta (chorionic villi), prostate (connective tissue), spinal cord (meningeal capillary vessel walls/collagen fiber tissue), spleen (red pulp capillary vessel walls), endometrium	4.2.3.7.7-2

5.6.3 Photosafety

No photosafety studies were conducted for belantamab mafodotin. Although mcMMAF absorbed light at wavelengths 290 to 700 nm, the molar extinction coefficient was <1,000 L/mol/cm. The applicant explained that belantamab mafodotin is unlikely to be phototoxic.

5.6.4 Cytokine release

An *in vitro* cytokine release study using human PBMC and a study to evaluate agonist activity on BCMA-positive cells were conducted (Table 21). Belantamab induced cytokine in human PBMC in the presence of NCI-H929 MM cells and imparted agonist activity on BCMA-positive cells.

Based on the above results, the applicant explained that when belantamab mafodotin is administered, cytokine release may occur as a result of secondary inflammation caused by the cytotoxic effects of cys-mcMMAF.

Whether cautionary statements regarding cytokine release-related events are necessary will be discussed in Section "7.R.3.9 Infusion reaction" taking into account the incidence of adverse events in the clinical studies.

Table 21. Cytokine release study

Test system	Method	Results	CTD
Human PBMC and NCI-H929 cells[*1]	**Cytokine measurement** Human PBMC was cultured with or without NCI-H929 cells. After being incubated with belantamab (0.1, 1, or 10 μg/mL), cytokine was measured **Evaluation of agonist activity on BCMA-positive cells** After incubating NCI-H929 cells with belantamab (0.1, 1, or 10 μg/mL) in the presence/absence of anti-human IgG, NF-κβ activity was measured	**Cytokine measurement** In the presence of NCI-H929 cells, release of IFN-γ, TNF-α, and IL-8 was detected **Evaluation of agonist activity on BCMA** NF-κβ activity increased in the presence of anti-human IgG	4.2.3.7.2-1 (reference data)

*1, a MM cell line

5.6.5 Mechanistic ocular toxicity

The mechanism by which belantamab mafodotin causes ocular toxicity was investigated in *in vitro* and *in vivo* studies (Table 22).

Belantamab mafodotin increased apoptosis concentration-dependently *in vitro* in human corneal epithelial cells (HCEC)

In an *in vivo* study using rabbits, neovascularization and inflammatory changes were observed in the superficial corneal layer or corneal stroma. Belantamab mafodotin and cys-mcMMAF were detected in tear fluid.

Table 22. Mechanistic ocular-toxicity studies

Test system	Method	Results	CTD
HCEC and RPTEC	Expression of BCMA in HCEC and RPTEC was evaluated by RT-qPCR	BCMA expression was not detected in HCEC or RPTEC	4.2.3.7.3-9 (reference data)
	Evaluation of apoptosis by belantamab mafodotin HCEC and RPTEC were incubated with belantamab mafodotin (0.1-577 μg/mL). Apoptosis was evaluated by measuring caspase 3/7 activity **Evaluation of cell viability by belantamab mafodotin** HCEC and RPTEC were incubated with belantamab mafodotin (0.1-577 μg/mL) and cell viability was evaluated **Evaluation of uptake mechanism** HCEC and RPTEC were pre/co-treated with EIPA (3-12.5 μM), and then incubated with belantamab mafodotin or belantamab (HCEC: 1-100 μg/mL or RPTEC: 10-300 μg/mL). Apoptosis was evaluated by measuring caspase 3/7 activity.	**Evaluation of apoptosis induction** HCEC, apoptosis increased in the belantamab mafodotin group (≥30 μg/mL) RPTEC, apoptosis increased in the belantamab mafodotin group (≥100 μg/mL) **Evaluation of cell viability** The minimum effective concentration (MEC) for the reduction of cell viability was as follows: • HCEC, belantamab mafodotin 50.4 μg/mL • RPTEC, belantamab mafodotin 70.7 μg/mL **Evaluation of uptake mechanism** HCEC: in the belantamab mafodotin group (≥50 μg/mL), pre/co-treatment with EIPA (≥6 μM) decreased the increase in apoptosis. No change in cell viability with or without EIPA pre/co-treatment. RPTEC: in the belantamab mafodotin group (≥150 μg/mL), pre/co-treatment with EIPA (25 μM) decreased the increase in apoptosis. No change in cell viability with or without EIPA pre/co-treatment. In the belantamab group, there were no changes in apoptosis or cell viability for HCEC and RPTEC with or without EIPA pre/co-treatment.	4.2.3.7.3-1 (reference data)
	HCEC and RPTEC were treated with cys-mcMMAF (0.1-100 μg/mL). The cytotoxic effects were evaluated by measuring nuclei count	HCEC, at ≥0.5 μg/mL, cys-mcMMAF dose-dependently decreased cell nuclei RPTEC, at ≥10 μg/mL, cys-mcMMAF dose-dependently decreased cell nuclei	4.2.3.7.3-3 (reference data)
Female rabbits (New Zealand White)	Belantamab mafodotin (0,[*1] 15, or 30 mg/kg) was administered intravenously QW for 2 or 4 weeks. Ophthalmologic examination and histopathological examination were performed	30 mg/kg/week × 4 weeks: corneal epithelial single cell necrosis, superficial corneal haze 15 mg/kg/week × 4 weeks: increased mitotic figures in the corneal epithelium, striations in the retina[*3]	4.2.3.2-8 (reference data)
Female rabbits (Dutch Belted)	Belantamab mafodotin (0,[*1] or 30[*2] mg/kg) was administered intravenously QW for 7 weeks. Ophthalmologic examination and histopathological examination were performed	Superficial corneal haze/neovascularization, conjunctival hyperemia, corneal haze/opacity, corneal size reduction, corneal epithelial single cell necrosis; in the corneal stroma, neovascularization/inflammation/mixed inflammatory cell infiltration/edema/congestion/pyknosis Belantamab mafodotin and cys-mcMMAF were detected in tear fluid	4.2.3.2-9 (reference data)

*1, a 25 mmol/L aqueous citrate buffer containing 0.05 mmol/L EDTA, 200 mmol/L trehalose, and 0.02% polysorbate 80; *2, Due to decreased body weight gain and decreased body weight, the fifth to seventh doses were reduced to 15 mg/kg; *3, Because there were no correlated histopathological findings, and no retinal findings were observed in other animal species [see Section 5.2] or in rabbits treated with belantamab mafodotin for a longer period of time (CTD4.2.3.2-9), it was determined that retinal striations observed were not clearly related to belantamab mafodotin.

5.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about the toxicity of belantamab mafodotin is acceptable.

5.R.1 Ocular toxicity

The applicant's explanation about the mechanism of ocular toxicity (abnormal findings of the cornea) observed in rats and rabbits after administration of belantamab mafodotin:

In rats, neither belantamab mafodotin nor cys-mcMMAF was distributed in the cornea. However, given that belantamab mafodotin was distributed in plasma and tear fluid [see Section 4.2.1], it is suspected that ocular toxicity is caused by uptake of belantamab mafodotin transported in plasma and tear fluid in the cornea. Although cys-mcMMAF also was distributed in plasma and tear fluid [see Section 4.2.1], given the low cell membrane permeability of cys-mcMMAF due to its charged C-terminal phenylalanine residue, and the plasma or tear fluid concentrations of cys-mcMMAF, lower than those of belantamab mafodotin [see Section 4.2.1], the effects of cys-mcMMAF on the cornea are considered to be negligible.

In the *in vitro* mechanistic ocular toxicity studies, no BCMA expression was detected in HCECs. In addition, belantamab mafodotin-mediated apoptosis was reduced in HCECs pre/co-treated with 5-(N-Ethyl-N-isopropyl)amiloride (EIPA), which is known to inhibit macropinocytosis [see Section 5.6.5]; therefore, the uptake of belantamab mafodotin in HCECs may be mediated by endocytic pathways rather than BCMA. Treatment with belantamab did not increase apoptosis in HCECs with or without EIPA pre/co-treatment [see Section 5.6.5], suggesting that ocular toxicity following administration of belantamab mafodotin is caused by the cytotoxic effect of the payload, MMAF.

Taken together, it is considered that the mechanism of ocular toxicity of belantamab mafodotin is as follows. Belantamab mafodotin reached the cornea through the vascular system or tear fluid in the corneal limbus, and belantamab mafodotin is internalized into HCECs mediated by the endocytic, non-specific uptake pathway rather than BCMA (e.g., *Cancer Res.* 2018;78:2115-26). Accumulation of cys-mcMMAF released from belantamab mafodotin causes corneal epithelium damage via microtubule polymerase inhibition and apoptosis induction by cys-mcMMAF. The damaged corneal epithelial cells migrate from the basal layer of the corneal epithelium toward the central cornea, which may be manifested as clinical symptoms including weakening eyesight, and these changes can be observed on slit lamp microscopy as corneal epithelial microcysts or keratopathy in humans (*Ophthalmol Ther.* 2020;9:889-911, *Curr Ophthalmol Rep.* 2024;12:13-22). These events are expected to be reversible through corneal epithelial cell turnover if doses are suspended. Ocular toxicity similar to that of belantamab mafodotin is reported with other ADCs containing MMAF as a payload (e.g., SGN-75, SGN-CD19A) (*Invest New Drugs.* 2014;32:1246-57, *Invest New Drugs.* 2018;36:121-35).

Presumably, non-specific internalization of belantamab mafodotin into cells via endocytosis can occur not only in the eye but also in other organs. However, given that presence of belantamab mafodotin in the tear fluid [see Section 5.6.5] promotes migration and accumulation of belantamab mafodotin in corneal cells, and that avascular nature of corneal epithelium has high non-specific endocytosis activity for nutrient and growth factor uptake from the surrounding environment (*Invest Ophthalmol Vis Sci*. 2017;58:416-23), it is possible that uptake of belantamab mafodotin in the cornea may have increased and cytotoxicity may have become more apparent.

PMDA's view:

The applicant's explanation about ocular toxicity mechanism was acceptable. The safety of these toxicity findings in humans will be discussed in Section "7.R.3.2 Eye disorders" taking into account the incidence of ocular events, etc. in the clinical studies.

5.R.2 Contraception for male patients

The applicant's explanation about contraception for male patients treated with belantamab mafodotin:

It is considered that belantamab mafodotin is genotoxic and embryo-fetal toxic based on an aneugenic mechanism [see Sections 5.3 and 5.5] and IgG can be distributed in semen (*Reprod Toxicol*. 2016;59:22-30). In addition, NOAEL or the no-observed effect level (NOEL) for the embryo-fetal development toxicity or the aneugenicity of belantamab mafodotin was not studied, and the safety margin based on the estimated belantamab mafodotin exposure through semen in the female partner was not determined. Therefore, exposure of the female partner to semen from a male patient receiving belantamab mafodotin may pose a risk of embryo-fetal development toxicity. Since spermatocytes always undergo meiosis, abnormal sperm is formed during the meiotic process of spermatocytes due to the aneugenicity of belantamab mafodotin, and if the sperm fertilizes an egg, there is a potential risk of harmful effects on embryo-fetal development. Based on the above, male patients with female partners of reproductive potential should use effective contraception for 6 months, i.e., 5 times the elimination half-life ($t_{1/2}$) of belantamab mafodotin in humans (14.3 days) plus 3 months (duration required for elimination of abnormal spermatocytes from the body) [see Section 5.5] in accordance with the "Guidance on the Need for Contraception Related to Use of Pharmaceuticals" (PSEHB/PED Notification No. 0216-1, dated February 16, 2023). This cautionary statement should be included in the package insert to ensure that the above instructions are followed.

PMDA accepted the applicant's explanation.

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

In this section, the term "total mAb" is used to refer to anti-BCMA antibody (belantamab) with or without cys-mcMMAF.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Belantamab mafodotin and the total mAb in human plasma were determined by ELISA[22)] (lower limit of quantification, 500 ng/mL for both, except for the DREAMM-1 and DREAMM-14 studies[23)]), and cys-mcMMAF in human plasma was determined by LC-MS/MS (lower limit of quantification,

22) In the analyses, belantamab mafodotin was captured using [redacted], and detected by [redacted] or [redacted]. Total mAb was captured using [redacted] or [redacted], and detected by [redacted].

23) In the DREAMM-14 study, 20 ng/mL (belantamab mafodotin only), in the DREAMM-1 study, 100 or 200 ng/mL for both belantamab mafodotin and the total mAb.

50 pg/mL). The ADA and neutralized antibodies in human serum were detected by ECL.

6.2 Clinical pharmacology

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.3.2-3, 5.3.3.2-4, DREAMM-11 study [ongoing since March 2019, data cut-off on November 25, 2021 (Part 1), April 6, 2023 (Part 2)])

An open-label, uncontrolled study was conducted in 15 patients with relapsed or refractory MM (15 subjects were included in the PK analyses) to investigate the PK and other aspects of belantamab mafodotin monotherapy, belantamab mafodotin/Bd, and belantamab mafodotin/Pd. The dosage regimens were as follows. In Part 1 (belantamab mafodotin monotherapy), belantamab mafodotin 2.5 or 3.4 mg/kg was administered as an intravenous infusion over at least 30 minutes Q3W in 21-day cycles; in Part 2A (belantamab mafodotin/Bd), belantamab mafodotin 2.5 mg/kg was administered as an intravenous infusion over at least 30 minutes Q3W in combination with Bd in 21-day cycles; in Part 2B (belantamab mafodotin/Pd), in combination with Pd in 28-day cycles, belantamab mafodotin 2.5 mg/kg on Day 1 in Cycle 1, and 1.9 mg/kg in Cycle 2 and subsequent cycles as an intravenous infusion over at least 30 minutes once every 4 weeks (Q4W). Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 23 and Table 24 show the PK parameters of belantamab mafodotin, total mAb, and cys-mcMMAF following administration of the first dose of belantamab mafodotin in Part 1. At both dose levels, the plasma concentrations of belantamab mafodotin and total mAb reached their C_{max} immediately after the end of infusion. The plasma cys-mcMMAF concentration reached its C_{max} by approximately 16 hours post-dose. The $t_{1/2}$ of belantamab mafodotin and total mAb at 2.5 mg/kg were similar to those at 3.4 mg/kg.

Table 23. Pharmacokinetic parameters of belantamab mafodotin and total mAb (belantamab mafodotin monotherapy)

Analyte	Dose (mg/kg)	N	C_{max} (µg/mL)	t_{max}*1 (h)	AUC_{tau} (µg·h/mL)	$t_{1/2}$ (days)
Belantamab mafodotin	2.5	4	36.4 (19.1)	2.60 (1.58, 3.68)	3,695 (26.3)	7.49 (8.96)
	3.4	4	41.3 (12.8)	1.64 (0.67, 1.68)	3,808 (41.8)*2	7.32 (27.6)*2
Total mAb	2.5	4	39.5 (17.0)	2.70 (1.62, 8.53)	6,358 (33.1)	9.03 (23.4)*2
	3.4	4	48.9 (14.1)	1.68 (0.63, 3.65)	7,144 (45.6)*2	7.46, 11.6*3

Geometric mean (coefficient of variation, %) (individual values for N = 2); *1, median (Min, Max); *2, N = 3; *3, N = 2

Table 24. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin monotherapy)

Dose (mg/kg)	N	C_{max} (pg/mL)	t_{max}* (h)	$AUC_{0\text{-}last}$ (pg·h/mL)
2.5	4	748 (30.5)	16.4 (8.55, 24.6)	73,341 (44.7)
3.4	4	2,797 (326)	16.2 (8.45, 24.1)	141,903 (77.0)

Geometric mean (coefficient of variation, %); *, median (Min, Max)

Table 25 and Table 26 show the PK parameters of belantamab mafodotin and cys-mcMMAF, respectively, following administration of the first dose of belantamab mafodotin in Part 2A and Part 2B.

Plasma belantamab mafodotin concentrations reached C_{max} rapidly, by approximately 0.7 hours post-dose, and plasma cys-mcMMAF concentrations reached C_{max} by approximately 22 hours post-dose.

Table 25. Pharmacokinetic parameters of belantamab mafodotin (in combination with Bd or Pd)

Part	N	C_{max} (μg/mL)	t_{max}* (h)	AUC_{tau} (μg·h/mL)	$t_{1/2}$ (days)
2A	3	47.6 (25.1)	0.780 (0.72, 1.85)	5,077 (13.1)	9.54 (15.5)
2B	4	61.7 (26.5)	1.87 (0.82, 2.20)	5,490 (25.4)	6.14 (59.7)

Geometric mean (coefficient of variation, %); *, median (Min, Max)

Table 26. Pharmacokinetic parameters of cys-mcMMAF (in combination with Bd or Pd)

Part	N	C_{max} (pg/mL)	t_{max}* (h)	$AUC_{0\text{-last}}$ (pg·h/mL)
2A	3	857 (33.0)	22.4 (22.1, 23.1)	80,090 (22.5)
2B	4	905 (28.4)	23.0 (22.0, 24.2)	82,630 (42.3)

Geometric mean (coefficient of variation, %); *, median (Min, Max)

6.2.2 Global clinical studies

6.2.2.1 Global phase III study (CTD 5.3.5.1-1, DREAMM-3 study [ongoing since April 2020, data cut-off on September 12, 2022])

An open-label, randomized study was conducted in 325 patients with relapsed or refractory MM (217 subjects were included in the PK analyses) to investigate the efficacy, safety, PK, and other aspects of belantamab mafodotin monotherapy. The dosage regimen was belantamab mafodotin 2.5 mg/kg as an intravenous infusion over at least 30 minutes Q3W. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 27 and Table 28 show the PK parameters of belantamab mafodotin, total mAb, and cys-mcMMAF following administration of the first dose of belantamab mafodotin. Both belantamab mafodotin and total mAb reached their C_{max} immediately after the end of infusion. The plasma cys-mcMMAF concentration reached its C_{max} at approximately 24 hours post-dose.

One of 195 patients tested positive for ADAs.

Table 27. Pharmacokinetic parameters of belantamab mafodotin and total mAb

Analyte	Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)
Belantamab mafodotin	2.5	102	44.0 (35.6)	1.64 (0.500, 24.0)	4,200 (39.7)*2
Total mAb	2.5	102	43.1 (32.3)	1.77 (0.500, 24.3)	6,650 (48.7)*3

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 66; *3, N = 78

Table 28. Pharmacokinetic parameters of cys-mcMMAF

Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max}*1 (h)	$AUC_{0\text{-}168}$ (ng·h/mL)
2.5	105	1.13 (65.5)	23.7 (0.500, 68.0)	104 (51.4)*2

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 76

6.2.2.2 Global phase III study (CTD 5.3.5.1-4, DREAMM-7 study [ongoing since May 2020, data cut-off on October 2, 2023])

An open-label, randomized study was conducted in 494 patients with relapsed or refractory MM (242 subjects were included in the PK analyses) to investigate the efficacy, safety, PK, and other aspects of belantamab mafodotin/Bd. The dosage regimen was belantamab mafodotin 2.5 mg/kg administered as an intravenous infusion over 30 to 60 minutes Q3W in combination with Bd. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 29 and Table 30 show the PK parameters of belantamab mafodotin and cys-mcMMAF following administration of the first dose of belantamab mafodotin. Belantamab mafodotin reached its C_{max} immediately after the administration while cys-mcMMAF concentration reached its C_{max} approximately 23 hours post-dose.

Thirteen of 234 patients tested positive for ADAs.[24)]

Table 29. Pharmacokinetic parameters of belantamab mafodotin (belantamab mafodotin/Bd)

N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)
73	46.8 (35.6)	1.43 (0.08, 2.77)	3,968 (32.6)*2

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 56

Table 30. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin/Bd)

N	C_{max} (ng/mL)	t_{max}*1 (h)	$AUC_{0\text{-}168}$ (ng·h/mL)
70	1.09 (48.1)	23.3 (0.7, 91.4)	95.1 (37.2)*2

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 59

6.2.2.3 Global phase III study (CTD 5.3.5.1-2, DREAMM-8 study [ongoing since October 2020, data cur-off on January 29, 2024])

An open-label, randomized study was conducted in 302 patients with relapsed or refractory MM (150 subjects were included in the PK analyses) to investigate the efficacy, safety, PK, and other aspects of belantamab mafodotin/Pd. The dosage regimen was belantamab mafodotin in combination with Pd in 28-day cycles. In Cycle 1, belantamab mafodotin 2.5 mg/kg and in Cycle 2 and subsequent cycles, belantamab mafodotin 1.9 mg/kg Q4W was administered as an intravenous infusion over at least 30 minutes. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 31 and Table 32 show the PK parameters of belantamab mafodotin and cys-mcMMAF, respectively, following administration of the first dose of belantamab mafodotin.

One of 144 patients tested positive for ADAs.

[24)] Among these patients, 12 had tested positive for ADAs before treatment with belantamab mafodotin

Table 31. Pharmacokinetic parameters of belantamab mafodotin (belantamab mafodotin/Pd)

N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)
57	47.5 (39.6)	1.75 (0.50, 163)	4,958 (25.8)*2

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 37

Table 32. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin/Pd)

N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-168} (ng·h/mL)
54	0.99 (50.5)	23.7 (0.5, 72.0)	85.3 (34.2)*2

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 41

6.2.3 Foreign clinical studies

6.2.3.1 Foreign phase I study (CTD 5.3.3.2-1, 5.3.3.2-2, DREAMM-1 study, dose escalation part [July 2014 to August 2019])

An open-label, uncontrolled study was conducted in 38 patients with relapsed or refractory MM (38 subjects were included in the PK analyses) to investigate the PK and other aspects of belantamab mafodotin monotherapy. The dosage regimen was belantamab mafodotin 0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, 2.5, 3.4, or 4.6 mg/kg administered as an intravenous infusion over 60 minutes Q3W. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 33 and Table 34 show the PK parameters of belantamab mafodotin, total mAb, and cys-mcMMAF following administration of the first dose of belantamab mafodotin. The C_{max} and AUC_{tau} of belantamab mafodotin, total mAb, and cys-mcMMAF generally increased dose-proportionally.

No patients tested positive for ADAs.

Table 33. Pharmacokinetic parameters of belantamab mafodotin and total mAb (belantamab mafodotin monotherapy)

Analyte	Dose (mg/kg)	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)	$t_{1/2}$ (days)
Belantamab mafodotin	0.03	1	429	2.08	—	—
	0.06	1	1,323	4.08	200	5.26
	0.12	4	2,957 (18)	1.19 (1.00, 2.00)	633 (35)	7.84 (37)
	0.24	4	4,548 (20)	3.09 (2.00, 8.78)	729 (91)	4.91 (76)*2
	0.48	3	11,876 (24)	1.00 (1.00, 4.00)	2,389 (51)	8.27 (50)
	0.96	3	23,050 (23)	2.05 (2.00, 2.08)	4,448 (80)	8.1, 15.1*3
	1.92	3	43,774 (45)	1.00 (0.50, 24.00)	9,893 (52)	12.9*4
	3.4	3	68,128 (21)	6.92 (2.02, 8.78)	22071, 24223*3	—
	4.6	6	117,386 (24)	1.56 (0.95, 2.07)	9,739 (39)	4.32 (17)*5
Total mAb	0.03	1	476	9.05	—	—
	0.06	1	1,440	2.07	160	3.59
	0.12	4	3,046 (16)	1.60 (1.17, 8.88)	550 (34)*2	8.14 (26)*2
	0.24	4	4,672 (19)	2.00 (1.03, 2.07)	583 (77)	5.76 (73)
	0.48	3	11,966 (25)	1.00 (1.00, 4.00)	1,729 (41)	7.04 (30)
	0.96	3	21,114 (12)	4.08 (2.05, 9.05)	3,285 (54)	5.3, 6.40*3
	1.92	3	45,231 (29)	1.00 (0.50, 2.00)	8781, 9281*3	8.37*4
	3.4	3	76,289 (18)	1.05 (0.97, 2.27)	12,973 (39)	6.43*4
	4.6	6	96,484 (18)	2.00 (1.00, 2.07)	12,945 (39)*6	7.60 (57)*5

Geometric mean (coefficient of variation, %) (individual values for N = 2); —, not calculated; *1, median (Min, Max); *2, N = 3; *3, N = 2; *4, N = 1; *5, N = 4; *6, N = 5

Table 34. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin monotherapy)

Dose (mg/kg)	N	C_{max} (pg/mL)	t_{max}*1 (h)	$AUC_{0\text{-last}}$ (pg·h/mL)
0.24	3	75.9 (19)	23.7 (9.00, 24.63)	1,335 (26)
0.48	3	181 (15)	24.7 (24.00, 25.83)	3,350 (19)
0.96	3	334 (38)	9.05 (8.78, 22.83)	9,231 (181)
1.92	3	715 (19)	8.75 (7.75, 24.00)	50,472 (17)
3.4	3	813 (35)	23.7 (23.17, 24.97)	76,529 (26)
4.6	6	1719 (87)	24.0 (7.83, 25.00)	121,340 (94)

Geometric mean (coefficient of variation, %); At all timepoints, concentrations at 0.03, 0.06, and 0.12 mg/kg were below the lower limit of quantification; *1, median (Min, Max)

6.2.3.2 Foreign phase I/II study (CTD 5.3.5.2-3, DREAMM-6 study, Arm B [ongoing since October 2018, data cut-off on February 28, 2023])

An open-label, uncontrolled study was conducted in 152 patients with relapsed or refractory MM (152 subjects were included in the PK analyses) to investigate the PK and other aspects of belantamab mafodotin/Bd.[25)] The dosage regimen was belantamab mafodotin in combination with Bd. In each 21-day cycle, belantamab mafodotin 1.9, 2.5, or 3.4 mg/kg Q3W or Q6W was administered as an intravenous infusion over 30 to 60 minutes. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 35 and Table 36 show the PK parameters of belantamab mafodotin and cys-mcMMAF following administration of the first dose of belantamab mafodotin.

One of 100 patients tested positive for ADAs.

Table 35. Pharmacokinetic parameters of belantamab mafodotin (belantamab mafodotin/Bd)

Dose (mg/kg)	Administration method	N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)
1.9	Stretch	12	52.2 (31.9)	1.90 (0.63, 22.5)	6,130 (23.8)*2
	Single	12	49.5 (21.4)	1.13 (0.55, 2.62)	4,452 (23.3)*3
2.5	Step-down stretch	12	61.2 (36.7)	2.03 (0.63, 26.0)	6,074 (37.1)*4
	Stretch	12	51.3 (26.0)	1.18 (0.62, 2.57)	5,396 (20.5)*2
	Split	13	21.3 (34.7)	1.23 (0.50, 2.22)	4,342 (22.4)*2
	Single*8	18	47.0 (23.2)	1.31 (0.45, 2.70)	5,014 (31.9)*5
3.4	Split	11	27.8 (37.3)	0.58 (0.50, 2.20)	5,702 (26.3)*6
	Single	16	64.0 (38.6)	2.00 (0.52, 3.83)	6,230 (35.0)*7

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 7; *3, N = 10; *4, N = 4; *5, N = 15; *6, N = 8; *7, N = 11; *8, the proposed regimen: Stretch method, belantamab mafodotin is administered every 2 cycles; Single method, belantamab mafodotin is administered on Day 1 of each cycle; Split method, administration of belantamab mafodotin is split between Day 1 and Day 8 of each cycle; Step-down stretch method, belantamab mafodotin 2.5 mg/kg is administered on Day 1 of Cycle 1, thereafter, belantamab mafodotin 1.9 mg/kg every 2 cycles

25) In this study, the PK of belantamab mafodotin in combination with lenalidomide and dexamethasone (Ld) was also investigated. However, given the proposed dosage regimen, only the results for belantamab mafodotin/Bd are presented in this section.

Table 36. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin/Bd)

Dose (mg/kg)	Administration method	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-168} (ng·h/mL)
1.9	Stretch	12	0.73 (29.9)*2	22.2 (22.1, 24.8)*2	—
	Single	12	0.75 (68.9)	24.5 (1.0, 25.8)	—
2.5	Step-down stretch	12	1.03 (52.8)	23.1 (22.0, 26.0)	89.1 (41.5)*3
	Stretch	12	1.29 (39.0)	22.4 (1.2, 74.0)	—
	Split	11	0.65 (88.0)	24.1 (19.3, 77.4)	52.8 (96.7)*4
	Single*6	11	1.15 (57.2)	24.1 (2.1, 25.3)	—
3.4	Split	11	1.03 (38.6)	24.6 (23.0, 70.3)	81.2 (31.5)*2
	Single	9	1.09 (40.3)	24.7 (21.9, 25.7)	—

Geometric mean (coefficient of variation, %); —, not calculated; *1, median (Min, Max); *2, N = 10; *3, N = 8; *4, N = 9; *6, proposed dosage regimen

6.2.3.3 Foreign phase II study (CTD 5.3.5.2-1, 5.3.5.2-2, DREAMM-2 study [June 2018 to March 2022])

An open-label, uncontrolled study was conducted in 221 patients with relapsed or refractory MM (218 subjects were included in the PK analyses) to investigate the PK and other aspects of belantamab mafodotin monotherapy. The dosage regimen was belantamab mafodotin 2.5 or 3.4 mg/kg Q3W as administered as an intravenous infusion over 30 minutes. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 37 and Table 38 show the PK parameters of belantamab mafodotin, total mAb, and cys-mcMMAF following administration of the first dose of belantamab mafodotin. The plasma concentrations of belantamab mafodotin and total mAb reached their C_{max} immediately after the end of infusion while plasma cys-mcMMAF concentration reached its C_{max} at approximately 24 hours post-dose. For both analytes, there were no marked differences in the PK parameters between formulations (frozen liquid or lyophilized powder).

One of 205 patients tested positive for ADAs, and this patient tested positive for neutralizing antibodies.

Table 37. Pharmacokinetic parameters of belantamab mafodotin and total mAb (belantamab mafodotin monotherapy)

Analyte	Dose (mg/kg)	N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)	$t_{1/2}$ (days)
Belantamab mafodotin	2.5	32	42.5 (26)	0.78 (0.42-2.50)	4,666 (46)*2	6.85 (46)*3
	3.4 (Frozen liquid)	21	52.0 (20)	0.70 (0.43-2.15)	5,678 (40)*4	6.91 (55)*5
	3.4 Lyophilized powder	22	51.3 (18)	0.75 (0.48-2.88)	5,946 (37)	8.18 (41)
Total mAb	2.5	30	48.9 (30)	1.75 (0.42-2.5)	7,305 (42)*3	10.1 (49)*3
	3.4 (Frozen liquid)	19	61.1 (27)	1.87 (0.50-24.5)	9,566 (42)*6	10.5 (70)*7
	3.4 Lyophilized powder	20	60.1 (18)	0.65 (0.48-2.17)	9,029 (40)*5	12.5 (61)*5

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 30; *3, N = 29; *4, N = 20; *5, N = 19; *6, N = 18; *7, N = 17

Table 38. Pharmacokinetic parameters of cys-mcMMAF (belantamab mafodotin monotherapy)

Dose (mg/kg)	N	C_{max} (pg/mL)	t_{max}*1 (h)	AUC_{0-168} (ng·h/mL)
2.5	27	903 (64)	22.8 (1.92, 65.6)	84.3 (59)*2
3.4 (Frozen liquid)	20	1,148 (65)	23.8 (17.4, 72.7)	109.4 (55)*3
3.4 (Lyophilized powder)	19	1,017 (61)	24.1 (0.97, 69.5)	81.6 (58)*4

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, N = 14; *3, N = 12; *4, N = 7

6.2.3.4 Foreign phase I study evaluating the effects of renal impairment on the PK of belantamab mafodotin and cys-mcMMAF (CTD 5.3.3.3-1, DREAMM-12 study, Part 1 [October 2020 to June 2022])

An open-label, uncontrolled study was conducted in 23 patients with relapsed or refractory MM (16 subjects were included in the PK analyses [8 subjects with normal renal function or mild renal impairment,[26)] 8 subjects with severe renal impairment]) to investigate the effects of renal function on the PK and other aspects of belantamab mafodotin.[27)] The dosage regimen was belantamab mafodotin 2.5 mg/kg administered as an intravenous infusion over 30 minutes Q3W. Plasma concentrations of belantamab mafodotin and other analytes were evaluated.

Table 39 and Table 40 show the PK parameters of belantamab mafodotin and cys-mcMMAF following administration of the first dose of belantamab mafodotin. The applicant considered that in addition to the PK parameters of belantamab mafodotin and cys-mcMMAF in patients with severe renal impairment (Table 39 and Table 40), given that renal impairment was not identified as a significant covariate for belantamab mafodotin and cys-mcMMAF in PPK analyses [see Section 6.2.5], it is unlikely that renal impairment will affect the PK of belantamab mafodotin and cys-mcMMAF.

Table 39. Pharmacokinetic parameters of belantamab mafodotin

Degree of renal impairment	N	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·h/mL)
Normal or mild*2	8	62.0 (38.4)	1.51 (0.65, 2.08)	4,379 (32.4)*3
Severe	8	47.6 (24.8)	3.00 (0.67, 7.40)	3,683 (32.6)

Geometric mean (coefficient of variation, %); *1, median (Min, Max); *2, patients with normal renal function or mild renal impairment, matched to severely renal impaired patients by baseline body weight and baseline albumin levels; *3, N = 4

Table 40. Pharmacokinetic parameters of cys-mcMMAF

Degree of renal impairment	N	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{0-168} (ng·h/mL)
Normal or mild *2	8	1.63 (64.0)	16.0 (0.92, 92.6)	135 (99.8)*3
Severe	8	0.71 (48.2)	23.4 (7.40, 30.7)	75.2 (48.2)

Geometric mean (coefficient of variation, %);*1, median (Min, Max); *2, patients with normal renal function or mild renal impairment, matched to severely renal impaired patients by baseline body weight and baseline albumin levels; *3, N = 6

26) Renal function was classified as follows: normal function or mild impairment, individual glomerular filtration rate (iGFR) (mL/min) ≥60; severe renal impairment, iGFR of 15 to 29. Individual glomerular filtration rates were calculated using the Modification of Diet in Renal Disease (MDRD) formula (*Ann Intern Med.* 2006; 154: 247-54).

27) This study consisted of Part 1 (patients with normal renal function or mild renal impairment [Group 1]; patients with severe renal impairment [Group 2]) and Part 2 (patients with end stage renal disease). Part 2 is ongoing.

In this study, samples of tear fluid were collected from patients to qualitatively assess the presence of belantamab mafodotin. Belantamab mafodotin was detected in the tear fluid of 14 subjects.

6.2.4 Relationship between exposure and change in QT/QTc interval

In the foreign phase I and II studies (DREAMM-1 and DREAMM-2 studies), the relationship between belantamab mafodotin, total mAb, or cys-mcMMAF and QT interval was evaluated based on a dataset of time-matched electrocardiogram data and plasma concentration of belantamab mafodotin and other analytes from 290 subjects. Following administration of 2.5 mg/kg or 3.4 mg/kg, the upper bound of the 90% confidence interval of the change in QTc or Fridericia-corrected QT interval (QTcF) at the C_{max} of belantamab mafodotin, total mAb, and cys-mcMMAF (146 μg/mL, 240 μg/mL, and 5,893 pg/mL, respectively) did not exceed 10 ms for all 3 analytes. There was no clear relationship between the plasma concentrations of belantamab mafodotin, total mAb, or cys-mcMMAF and QTc/QTcF.

Based on the above results, the applicant explained that it is unlikely that QT/QTc interval prolongation will occur when belantamab mafodotin is used in clinical settings.

6.2.5 PPK analyses

Population pharmacokinetic (PPK) analyses were performed using a nonlinear mixed effects model (software, NONMEM Version 7.3.0) based on the PK data for belantamab mafodotin and cys-mcMMAF from 977 subjects, at 8,880 timepoints (plasma belantamab mafodotin concentration) and 6,354 timepoints (plasma cys-mcMMAF concentration) from the foreign phase II study (DREAMM-2 study), global phase III study (DREAMM-3 study), foreign phase I study (DREAMM-12 study), foreign phase II study (DREAMM-14 study), foreign phase I/II study (DREAMM-6 study), and global phase III study (DREAMM-7 study).[28)] The PK of belantamab mafodotin was described by a linear two-compartment model with a time-varying decrease in total body clearance (CL) and the PK of cys-mcMMAF was described by a linear two-compartment model with a time-varying decrease in the drug-antibody ratio.

In this analysis, the following covariate effects were tested for belantamab mafodotin parameters: body weight, albumin, soluble BCMA (sBCMA), serum IgG, race, estimated glomerular filtration rate (eGFR), number of prior therapies, renal impairment, hepatic impairment, and myeloma immunoglobulin on CL; body weight, albumin, sBCMA, body mass index (BMI), race, and serum IgG on central volume of distribution (V1); BMI, race, albumin, serum IgG, sBCMA, and body weight on

28) Characteristics of patients included in the analyses, median (Min, Max), or the number of subjects in each category were as follows: body weight, 74.0 kg (37.0, 170); albumin, 39.0 g/L (19.0, 57.0); sBCMA, 56.0 μg/L (2.08, 2030); BMI, 26.7 kg/m^2 (14.0, 48.4); serum IgG, 13.1 (0.350, 119); race: White (N = 763), Asian (N = 133; including Japanese N = 15), Black (N = 61), Other (N = 8), Unknown (N = 12); eGFR, 75.6 mL/min (12.0, 150); renal impairment: Normal (N = 312), Mild impairment (N = 410), Moderate impairment (N = 225), Severe impairment (N = 27), End stage renal disease (N = 3); hepatic impairment: Normal (N = 826), Mild impairment (N = 116), Moderate impairment (N = 5), Severe impairment (N = 1), Unknown (N = 29); combination therapy: Monotherapy (N = 583), Combination with Bd (N = 349), Combination with LEN and DEX (N = 45); β2 microglobulin: 297 nmol/L (94.9, 5190); LDH, 198 U/L (59.0, 3020); myeloma immunoglobulin subtype: IgA (N = 206), IgG (N = 644), IgM (N = 6), Other (N = 8), Unknown (N = 113); number of prior therapies: 1 therapy (N = 158), 2 to 3 therapies (N = 288), >3 therapies (N = 531)

peripheral volume of distribution (V2); body weight on Q; IgG type, combination therapy, albumin, sBCMA, serum IgG, LDH, and β2 microglobulin on I_{max}; and IgG type, combination therapy, albumin, sBCMA, serum IgG, LDH, and β2 microglobulin on TI50. The following covariate effects were tested for cys-mcMMAF: body weight, albumin, sBCMA, serum IgG, race, eGFR, number of prior therapies, renal impairment, hepatic impairment, and myeloma immunoglobulin on CL; body weight, albumin, sBCMA, BMI, race, and serum IgG on V3. The following significant covariates were identified for belantamab mafodotin parameters: body weight, albumin, sBCMA, serum IgG, and race (Asian and Black/African American) on CL; body weight, albumin, sBCMA, and BMI on V1; body weight and albumin on V2; body weight on Q; combination therapy, serum IgG, and sBCMA on I_{max}. The following significant covariates were identified for cys-mcMMAF: sBCMA and body weight on CL; sBCMA, serum IgG, body weight, albumin, race (White, Asian, and Black/African American), and BMI on V3.

The below are the estimated average concentrations (C_{ave}) for belantamab mafodotin and cys-mcMMAF in Cycle 1 in the subpopulations for the subgroup analyses of body weight, sBCMA, albumin, BMI, and race, which were identified as covariates that would have significant effects on belantamab mafodotin and cys-mcMMAF. For both belantamab mafodotin and cys-mcMMAF, the C_{ave} in each sub-population for all the covariates was within the range of 0.8- to 1.25-fold the overall population; therefore, the applicant explained that it is unlikely that change in C_{ave} for belantamab mafodotin or cys-mcMMAF associated with these covariates will have adverse effects in clinical settings.

- body weight: the geometric means [95% CI] of C_{ave} for subpopulations 37 to 63.2 kg and 86.5 to 170.4 kg were 6.89 µg/mL [6.6, 7.2] and 8.9 µg/mL [8.6, 9.2], respectively, for belantamab mafodotin, and 0.232 ng/mL [0.22, 0.25] and 0.264 ng/mL [0.25, 0.28], respectively, for cys-mcMMAF.
- sBCMA: the geometric means [95% CI] of C_{ave} for subpopulations 2.08 to 21.78 µg/L and 147 to 2,026 µg/L were 9.46 µg/mL [9.2, 9.7] and 6.49 µg/mL [6.2, 6.8], respectively, for belantamab mafodotin, and 0.21 ng/mL [0.2, 0.22] and 0.284 ng/mL [0.27, 0.3], respectively, for cys-mcMMAF.
- albumin: the geometric means [95% CI] of C_{ave} for subpopulations 19 to 35 g/L and 42 to 57 g/L were 6.06 µg/mL [5.8, 6.3] and 9.25 µg/mL [9.0, 9.5], respectively, for belantamab mafodotin, and 0.272 ng/mL [0.26, 0.29] and 0.232 ng/mL [0.22, 0.25], respectively, for cys-mcMMAF.
- BMI: the geometric means [95% CI] of C_{ave} for subpopulations <18.5 and ≥30 were 5.94 µg/mL [5.0, 7.1] and 8.86 µg/mL [8.6, 9.2], respectively, for belantamab mafodotin, and 0.202 ng/mL [0.17, 0.24] and 0.266 ng/mL [0.25, 0.28], respectively, for cys-mcMMAF.
- race: the geometric means [95% CI] of C_{ave} for subpopulations "Asian," "Black or African American," and "White" were 7.57 µg/mL [7.1, 8.1], 8.63 µg/mL [8.0, 9.3], and 7.81 µg/mL [7.7, 8.0], respectively, for belantamab mafodotin, and 0.248 ng/mL [0.23, 0.27], 0.256 ng/mL [0.23, 0.29], and 0.242 ng/mL [0.24, 0.25], respectively, for cys-mcMMAF.

The applicant's explanation about combination therapy and serum IgG, which were identified as covariates that would have significant effects on belantamab mafodotin and cys-mcMMAF:

- Given that there were no clear differences in Cycle 1 exposure between belantamab mafodotin monotherapy and combination therapy with Bd or Pd [see Sections 6.2.2.1, 6.2.2.2, and 6.2.2.3], it is unlikely that combination therapy-associated change in C_{ave} of belantamab mafodotin will have adverse effects in clinical settings.
- The estimated geometric means [95% CI] of C_{ave} for belantamab mafodotin in serum IgG subpopulations 0.35 to 4.01 g/L and 27.39 to 118.77 g/L in Cycle 1 were 9.01 µg/mL [8.7, 9.3] and 5.91 µg/mL [5.7, 6.1], respectively, which suggested a trend towards a decrease in belantamab mafodotin exposure among patients with high serum IgG levels. However, an exposure-response analysis showed limited effects of the serum IgG-associated changes in C_{ave} of belantamab mafodotin on safety and efficacy; therefore, it is unlikely that serum IgG-associated changes in C_{ave} of belantamab mafodotin will have adverse effects in clinical settings. The estimated geometric means [95% CI] of C_{ave} for cys-mcMMAF in serum IgG subpopulations 0.35 to 4.01 g/L and 27.39 to 118.77 g/L in Cycle 1 were 0.23 ng/mL [0.22, 0.24] and 0.266 mg/mL [0.25, 0.28], respectively. Because these values were within the range of 0.8- to 1.25-fold the overall population, it is unlikely that serum IgG-associated changes in C_{ave} of cys-mcMMAF will have adverse effects in clinical settings.

6.2.6 Exposure-response relationship for efficacy and safety

6.2.6.1 Exposure-efficacy relationship

Based on data obtained from the DREAMM-7 and DREAMM-6 studies, the relationship between belantamab mafodotin exposure (e.g., C_{ave}) in Cycle 1 of belantamab mafodotin/Bd and the following endpoints were analyzed: overall response rate, very good partial response (VGPR) or better, complete response (CR) or better, minimal residual disease (MRD) negativity, PFS, duration of response (DoR), and time to response (TTR). The results indicated that is an increase in overall response, increase in VGPR or better, and reduction in time to response (TTR) were associated with an increase in belantamab mafodotin C_{ave}. However, CR or better, MRD negativity, PFS, and DoR were not clearly associated with belantamab mafodotin C_{ave}.

Based on data obtained from the DREAMM-8 study, the relationship between belantamab mafodotin C_{ave} in Cycle 1 of belantamab mafodotin/Pd and the following endpoints were analyzed: overall response rate, VGPR or better, CR or better, MRD negativity, PFS, DoR, and TTR. The results indicated that an increase in CR or better, increase in MRD negativity, and increase in VGPR or better were associated with an increase in belantamab mafodotin C_{ave}. However, overall response rate, PFS, DoR, and TTR were not clearly associated with belantamab mafodotin C_{ave}.

6.2.6.2 Exposure-safety relationship

Based on data obtained from DREAMM-6 (Arm B) and DREAMM-7 studies, the relationship between belantamab mafodotin exposure (C_{ave}) in Cycle 1 of belantamab mafodotin/Bd and the safety endpoints[29)] was analyzed. The results are as follows:

- Changes including the following were noted with increasing belantamab mafodotin C_{ave}: increase in the probability of Grade ≥2 or Grade ≥3 corneal adverse events, increase in the probability of Grade ≥3 best corrected visual acuity (BCVA) events,[30)] increase in the probability of Grade ≥2 findings in ophthalmologic examination, and increase in the probability of worsening of BCVA for the best eye as defined by ΔlogMar ≥0.3. In addition, with increasing belantamab mafodotin maximum concentration (C_{max}), the probability of Grade ≥2 BCVA events and the probability of Grade ≥3 findings in ophthalmologic examination increased. Conversely, Grade ≥2 or Grade ≥3 ocular adverse events of special interest, and unilateral or bilateral worsening of BCVA to 20/50 or worse were not clearly associated with belantamab mafodotin C_{ave}.
- There was an increase in non-ocular adverse events that led to an increase in dose interruption with increasing belantamab mafodotin C_{max}. However, the probability of Grade ≥3 thrombocytopenia, the probability of Grade 3 or 4 adverse events, the probability of treatment discontinuation, and the probability of dose reduction were not clearly associated with belantamab mafodotin C_{ave}.
- Probabilities of the safety endpoints were not clearly associated with cys-mcMMAF C_{ave}.

Based on the data obtained from the DREAMM-8 study, the relationship between belantamab mafodotin C_{ave} and other parameters and the safety endpoints[29)] in belantamab mafodotin/Pd was analyzed. The results are as follows:

- A reduction in the time to initial onset of Grade ≥2 ocular adverse events of special interest and a reduction in the time to initial onset of Grade ≥2 corneal adverse events were noted with increasing belantamab mafodotin C_{ave}. Probabilities of Grade ≥2 corneal events and of Grade ≥2 corneal examination findings increased and time to onset of Grade ≥2 corneal examination findings decreased with increasing blood belantamab mafodotin concentrations on Day 28 of Cycle 1. However, the probability of Grade ≥2 or Grade ≥3 ocular adverse events of special interest, the probability of worsening of BCVA for the best eye as defined by ΔlogMar ≥0.3, and bilateral worsening of BCVA to 20/50 or worse were not clearly associated with belantamab mafodotin C_{ave}.
- Regarding non-ocular adverse events, the probability of Grade ≥3 thrombocytopenia and serious adverse events were not clearly associated with belantamab mafodotin C_{ave}.

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29) Grade ≥2 or Grade ≥3 ocular adverse events of special interest, time to initial onset of Grade ≥2 or Grade ≥3 ocular adverse events of special interest, Grade ≥2 or Grade ≥3 corneal events, time to initial onset of Grade ≥2 or Grade ≥3 corneal events, Grade ≥2 or Grade ≥3 BCVA events, time to initial onset of Grade ≥2 or Grade ≥3 BCVA events, Grade ≥2 or Grade ≥3 corneal examination findings, time to initial onset of Grade ≥2 or Grade ≥3 corneal examination findings, the probability of worsening of BCVA for the best eye as defined by ΔlogMar ≥0.3, the probability of unilateral or bilateral worsening of BCVA to 20/50 or worse, the probability of treatment discontinuation, the probability of dose reduction, adverse events leading to dose reduction, the probability of dose interruption, Grade 3 or 4 adverse events, serious adverse events, Grade ≥3 thrombocytopenia, and infusion reaction. In the DREAMM-7 study, the incidence of "adverse events leading to dose reduction" was ≥90%, the incidence of "infusion reaction" and that of "serious adverse events" were ≤10%; therefore, these were not included in the analysis. In the DREAMM-8 study, the incidence of Grade 3 or 4 adverse events was ≥90%, and the incidence of "infusion reaction" was ≤10%; therefore, these were not included in the analysis.

30) Ocular adverse events based on the Keratopathy Visual Acuity (KVA) scale.

- Probabilities of the safety endpoints were not clearly associated with cys-mcMMAF C_{ave}.

6.2.7 Differences in PK between Japanese and non-Japanese populations

The applicant explained that taking into account the factors including the findings below, there are no clear differences in the PK of belantamab mafodotin, total mAb, and cys-mcMMAF between Japanese and non-Japanese populations.

- In the DREAMM-3 study, in which belantamab mafodotin was administered alone, there were no marked differences between Japanese and non-Japanese populations in the PK parameters of belantamab mafodotin, total mAb, and cys-mcMMAF following administration of belantamab mafodotin (Table 41 and Table 42).
- In the PPK analyses, race did not have a clinically relevant effect on the PK parameters of belantamab mafodotin or cys-mcMMAF [see Section 6.2.5].

Table 41. Pharmacokinetic parameters of belantamab mafodotin and total mAb in the DREAMM-3 study

Analyte	Race	N	C_{max} (μg/mL)	AUC_{tau} (μg·h/mL)
Belantamab mafodotin	Japanese	12	41.4 (19.9)	4,590 (32.1)[*1]
	Non-Japanese	90	44.4 (37.3)	4,140 (40.9)[*2]
Total mAb	Japanese	12	42.6 (27.0)	7,430 (39.0)[*3]
	Non-Japanese	90	43.2 (33.0)	6,540 (50.1)[*4]

Geometric mean (coefficient of variation, %); *1, N = 9; *2, N = 57; *3, N = 10; *4, N = 68

Table 42. Pharmacokinetic parameters of cys-mcMMAF in the DREAMM-3 study

Race	N	C_{max} (ng/mL)	$AUC_{0\text{-}168}$ (ng·h/mL)
Japanese	12	0.968 (76.3)	73.2 (40.3)[*1]
Non-Japanese	93	1.15 (64.2)	109 (50.6)[*2]

Geometric mean (coefficient of variation, %); *1, N = 9; *2, N = 67

6.R Outline of the review conducted by PMDA

Based on the submitted data and discussions below, PMDA concluded that the applicant's explanation about the clinical pharmacology, etc. of belantamab mafodotin is acceptable.

6.R.1 Use of belantamab mafodotin in patients with hepatic impairment

The applicant's explanation about the use of belantamab mafodotin in patients with hepatic impairment:
No clinical studies were conducted to evaluate the effects of hepatic impairment on the PK of belantamab mafodotin and cys-mcMMAF in patients with hepatic impairment; however, taking into consideration the factors below, it is unlikely that the decrease in hepatic function will affect the PK of belantamab mafodotin or cys-mcMMAF. Therefore, it is considered that dose adjustment of belantamab mafodotin for patients with hepatic impairment will be unnecessary.

- Belantamab mafodotin is an ADC composed of belantamab, a monoclonal antibody targeting BCMA, that is conjugated to cys-mcMMAF. Belantamab is eliminated via proteolytic degradation pathways, etc., while the metabolism of cys-mcMMAF is primarily characterized by non-enzymatic transformation and is excreted in feces [see Section 4.4].

- In the PPK analyses, hepatic impairment was not identified as a significant covariate affecting the PK parameters of belantamab mafodotin or cys-mcMMAF [see Section 6.2.5]. Based on the results of the PPK analyses, in patients with hepatic impairment (normal, 826 subjects; mild, 116 subjects; moderate, 5 subjects), the estimated geometric means [95% CI] of C_{ave} in Cycle 1 were 7.12 μg/mL [6.7, 7.6] (mild) and 7.26 μg/mL [5.1, 10] (moderate) for belantamab mafodotin, and 0.276 ng/mL [0.25, 0.30] (mild) and 0.246 ng/mL [0.17, 0.36] (moderate) for cys-mcMMAF, which are within the range of 0.8- to 1.25-fold the results for the overall population (belantamab mafodotin, 7.83 μg/mL [7.7, 8.0]; cys-mcMMAF, 0.243 ng/mL [0.24, 0.25]).

PMDA accepted the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from the studies summarized in Table 43.

Table 43. List of clinical studies on efficacy and safety

Data category	Location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japan	DREAMM-11	I	Patients with relapsed or refractory MM	15	Part 1 Belantamab mafodotin 2.5 or 3.4 mg/kg was administered IV Q3W Part 2 Arm A: in combination with Bd,[*1] belantamab mafodotin 2.5 mg/kg was administered IV Q3W Arm B: in combination with Pd,[*2] belantamab mafodotin 2.5 mg/kg was administered IV Q4W in Cycle 1, and 1.9 mg/kg IV Q4W in subsequent cycles	Tolerability Safety
	Global	DREAMM-7	III	Patients with relapsed or refractory MM	(1) 243 (2) 251 (3) 10 (4) 14	Main cohort (1) Belantamab mafodotin/Bd: in combination with Bd,[*1] belantamab mafodotin 2.5 mg/kg was administered IV Q3W (2) DAR/Bd: in combination with Bd,[*1] DAR[*3] was administered Japan extension cohort (3) Belantamab mafodotin/Bd: in combination with Bd,[*1] belantamab mafodotin 2.5 mg/kg was administered IV Q3W (4) DAR/Bd: in combination with Bd,[*1] DAR[*3] was administered	Efficacy Safety
		DREAMM-8	III	Patients with relapsed or refractory MM	(1) 155 (2) 147 (3) 10 (4) 11	Main cohort (1) Belantamab mafodotin/Pd: in combination with Pd,[*2] belantamab mafodotin 2.5 mg/kg was administered IV Q4W in Cycle 1, and 1.9 mg/kg IV Q4W in subsequent cycles (2) VPd: VPd[*4] was administered Japanese cohort, including part of (1) and (2) (3) Belantamab mafodotin/Pd: in combination with Pd,[*2] belantamab mafodotin 2.5 mg/kg was administered IV Q4W in Cycle 1, and 1.9 mg/kg IV Q4W in subsequent cycles (4) VPd: VPd[*4] was administered	Efficacy Safety

Data category	Location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoints
		DREAMM-3	III	Patients with relapsed or refractory MM	(1) 218 (2) 107	(1) Belantamab mafodotin: belantamab mafodotin 2.5 mg/kg was administered IV Q3W (2) Pd: Pd[*2] was administered	Efficacy Safety
	Foreign	DREAMM-1	I	Patients with relapsed or refractory MM	73	Dose-escalation part: belantamab mafodotin 0.03 to 4.6 mg/kg was administered IV Q3W Dose-expansion part: belantamab mafodotin 3.4 mg/kg was administered IV Q3W	Tolerability Safety
		DREAMM-6 (Arm B)	I/II	Patients with relapsed or refractory MM	107	Dose-escalation part: in combination with Bd,[*1] belantamab mafodotin 2.5 or 3.4 mg/kg was administered IV Q3W Dose-expansion part: in combination with Bd,[*1] belantamab mafodotin 1.9 to 3.4 mg/kg was administered using 4 different dosing schedules[*5]	Tolerability Safety Efficacy
		DREAMM-2	IIb	Patients with relapsed or refractory MM	221	Belantamab mafodotin 2.5 or 3.4 mg/kg was administered IV Q3W	Efficacy Safety
Reference	Foreign	DREAMM-12	I	Renal-impaired patients with relapsed or refractory MM	23	Belantamab mafodotin 2.5 mg/kg was administered IV Q3W	Safety PK

*1, in 21-day cycles, on Days 1, 4, 8, and 11, BOR 1.3 mg/m² was administered SC (IV administration was allowed only in the DREAMM-6 study), and on Days 1, 2, 4, 5, 8, 9, 11, and 12, DEX 20 mg was administered once daily PO or IV (8 cycles total); *2, in 28-day cycles, POM 4 mg was administered PO once daily on Days 1 to 21, and DEX 40 mg PO on Days 1, 8, 15, and 22 (IV administration was allowed only in the DREAMM-11 study); *3, in 21-day cycles (28-day cycles in Cycle 9 and thereafter), DAR 16 mg/kg was administered QW in Cycles 1 to 3, Q3W in Cycles 4 to 8, and Q4W in Cycle 9 and thereafter; *4, in 21-day cycles, POM 4 mg was administered PO on Days 1 to 14, and BOR 1.3 mg/m² was administered SC on Days 1, 4, 8, and 11 (Days on 1 and 8 in Cycle 9 and thereafter), and DEX 20 mg was administered PO on Days 1, 2, 4, 5, 8, 9, 11, and 12 (Days 1, 2, 8, and 9 in Cycle 9 and thereafter); *5, see Footnote 66

The following sections summarize the clinical studies. Main adverse events other than deaths that occurred in the clinical studies are described in Section "7.3 Adverse events and other findings observed in clinical studies."

7.1 Evaluation data

7.1.1 Japanese phase I study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2-3, 5.3.3.2-4, DREAMM-11 study [ongoing since March 2019, data cut-off on November 25, 2021 (Part 1), April 6, 2023 (Part 2)])

An open-label, uncontrolled study was conducted at 4 study centers (3 study centers in Part 1 and 4 study centers in Part 2) in patients with relapsed or refractory MM[31)] (target sample size, 24 subjects) to investigate the safety and other aspects of belantamab mafodotin monotherapy, belantamab mafodotin/Bd, and belantamab mafodotin/Pd.

The DREAMM-11 study investigated belantamab mafodotin monotherapy (Part 1) and the combination therapy of belantamab mafodotin (Part 2A and Part 2B) with the following regimens.

31) Eligible patients were those who had ≥2 prior lines of anti-MM regimens (including ≥1 regimen of proteasome inhibitors and ≥1 regimen of immunomodulators) in Part 1, and those who had ≥1 prior line of anti-MM regimens in Part 2 (patients with intolerance/refractoriness to BOR [Part 2A] and patients with prior POM treatment [Part 2B] were excluded).

Part 1: patients were to receive belantamab mafodotin 2.5 or 3.4 mg/kg intravenously Q3W in 21-day cycles
Part 2A: patients were to receive belantamab mafodotin 2.5 mg/kg intravenously Q3W in 21-day cycles in combination with Bd[32)]
Part 2B: patients were to receive belantamab mafodotin 2.5 mg/kg in Cycle 1 and 1.9 mg/kg in subsequent cycles, administered intravenously Q4W in combination with Pd, in 28-day cycles[33)]

All 15 subjects enrolled in the study (8 subjects in Part 1, 3 subjects in Part 2A, and 4 subjects in Part 2B) received belantamab mafodotin and were included in the safety analysis set, with 14 subjects (7 subjects in Part 1, 3 subjects in Part 2A, and 4 subjects in Part 2B) being evaluated for dose limiting toxicity (DLT).

The first cycle in each part was defined as the evaluation period for DLT. Since only 1 subject in Part 2B experienced DLT (liver injury), it was determined that belantamab mafodotin monotherapy, belantamab mafodotin/Bd, and belantamab mafodotin/Pd in Japanese patients are tolerable regimens.[34)]

During study drug treatment or within 30 days of the last dose, 1 of 8 subjects (12.5%) in Part 1 died of disease progression. In Part 2, there were no deaths during study drug treatment or within 30 days of the last dose.

7.1.2 Global studies

7.1.2.1 Global phase III study (CTD 5.3.5.1-4, 5.3.5.1-5, DREAMM-7 study, main cohort [ongoing since May 2020, data cut-off on October 2, 2023] Japan expansion cohort [ongoing since July 2021, data cut-off on April 3, 2024])

An open-label, randomized study was conducted at 142 study centers in 20 countries and regions including Japan in patients with relapsed or refractory MM[35)] (target sample size, 478 subjects[36)]) to compare the efficacy and safety of belantamab mafodotin/Bd and daratumumab (DAR)/Bd. A Japan expansion cohort was established separately from the main cohort of this study to enroll additional Japanese patients. Unless otherwise noted, the results of the main cohort are presented as the results of

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32) Subjects were to receive BOR 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11 and DEX 20 mg once daily orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 in each cycle for a total of 8 cycles.
33) Subjects were to receive POM 4 mg orally on Days 1 to 21, and DEX 40 mg orally or intravenously on Days 1, 8, 15, and 22.
34) In Part 2B, it was initially planned that if 1 of the first 3 subjects developed DLT, an additional 3 subjects would be enrolled. However, after 1 subject had been enrolled, the result data from other clinical studies of belantamab mafodotin available at that time indicated no safety concerns specific to Japanese patients associated with belantamab mafodotin/Pd treatment. Accordingly, enrollment in Part 2B was concluded after the enrollment of 4 patients.
35) Patients with ≥1 prior line of an anti-MM regimen were included. Patients who were intolerant to DAR or BOR, resistant to anti-CD38 monoclonal antibody drugs or BOR, or with prior anti-BCMA therapy were excluded.
36) The primary endpoint of this study was PFS determined by an independent review committee. Assuming a hazard ratio of 0.67 for belantamab mafodotin/Bd versus DAR/Bd (corresponding to median PFS values of 25 and 16.7 months, respectively) and a one-sided significance level of 2.5%, approximately 280 PFS events provided 92% power to detect a difference between the treatment groups . Considering the duration of the follow-up period and other factors, a target sample size of 478 subjects was set.

the DREAMM-7 study. The results of the Japan expansion cohort are presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety."

The patients in the belantamab mafodotin/Bd group received treatment in 21-day cycles. Belantamab mafodotin 2.5 mg/kg Q3W was administered as an intravenous infusion over at least 30 minutes in combination with Bd.[37] In the DAR/Bd group, DAR[38] was to be administered. In both groups, after the end of administration of Bd, belantamab mafodotin or DAR was to be continued until disease progression or the treatment discontinuation criteria were met.

Subjects who were enrolled in this study and randomized (494 subjects total[39]; 243 subjects in the belantamab mafodotin/Bd group and 251 subjects in the DAR/Bd group) were included in the intent-to-treat (ITT) population, which was also the efficacy analysis set (including 2 Japanese patients in the belantamab mafodotin/Bd group). Of the ITT population, 6 subjects who did not receive the study drug (1 subject in the belantamab mafodotin/Bd group and 5 subjects in the DAR/Bd group) were excluded and the remaining 488 subjects (242 subjects in the belantamab mafodotin/Bd group and 246 subjects in the DAR/Bd group) were included in the safety analysis set, which included 2 Japanese subjects in the belantamab mafodotin/Bd group.

The primary endpoint for this study was PFS determined by an independent review committee according to the International Myeloma Working Group (IMWG) criteria (*Lancet Oncol.* 2016;17:e328-46).[40] Table 44 shows the main amendment to the statistical analysis plan for this study related to the primary endpoint. The interim analysis (data cut off date, October 2, 2023) added to Protocol Amendment 6 (dated September 20, 2023) was positioned as the primary analysis.

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[37] Subjects were to receive BOR 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11 and DEX 20 mg once daily orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 in each cycle for a total of 8 cycles (DEX 20 mg was to be reduced to 10 mg for patients who were aged >75 years, who had a BMI <18.5 kg/m^2, who had previous unacceptable adverse drug reactions associated with glucocorticoid therapy, or who were unable to tolerate the starting dose).

[38] In 21-day cycles (28-day cycles from Cycle 9 onward), DAR 16 mg/kg was to be administered intravenously QW in Cycles 1 to 3, Q3W in Cycles 4 to 8, and Q4W in Cycle 9 onward.

[39] Two subjects who were randomized to the DAR/Bd group but did not receive treatment were re-screened and then re-randomized (1 subject each in the belantamab mafodotin/Bd group and the DAR/Bd group). In the ITT population, these 2 subjects were handled as 4 subjects, and the randomization was maintained.

[40] The PFS was defined as the time from randomization to the date of disease progression first recorded by the independent review committee or death from any cause whichever is earlier. Patients who met the following were to be censored at the applicable date.

- Randomization date for patients with no adequate post-baseline assessment before the start of new anti-MM pharmacotherapy who had no documented disease progression or had not died.
- Date of last disease assessment for patients with adequate post-baseline assessment who had no documented disease progression or had not died, and started new anti-MM pharmacotherapy.
- Randomization date for patients with no post-baseline assessment who had documented disease progression or had died after extended loss-to-follow-up period; or appropriate assessment date for patients with post-baseline assessment.

Table 44. Main changes in statistical analysis plan (DREAMM-7 study)

Protocol	Original version	Amendment 3	Amendment 5	Amendment 6
Date	[redacted]			
Details and reasons for amendment	—	Because patient enrollment had been completed before the first interim analysis, the first interim analysis was removed, and the number of PFS events required was updated accordingly.	To characterize more adequately, the overall benefits and risks including eye disorders, the interim analysis was removed, and the number of PFS events required was updated accordingly.	Because the US regulatory authorities request for higher than initially planned maturity of OS data at the time the primary PFS results would be obtained, the timing of final analysis was delayed by 4 to 6 months, and an interim analysis was added.
Interim analyses and objective	First: harm Second: futility and efficacy	Futility and efficacy	—	Efficacy
Time of interim analyses	First: PFS events: ≈ 67 events (≈ 25%) Second: PFS events: ≈ 187 events (≈ 70%)	PFS events: ≈ 214 events (≈ 80%)	—	PFS events: ≈ 250 events (≈ 89%)
Time of final analysis	PFS events: 267 events	PFS events: 268 events	PFS events: 259 events	PFS events: 280 events
Multiplicity adjustment procedure	Haybittle-Peto approach	No change	—	Lan-DeMets approach approximating the O'Brien-Fleming α spending function

—, not applicable

Table 45 shows the primary endpoint, PFS determined by an independent review committee according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46), and Figure 3 shows Kaplan-Meier curves. The results demonstrated the superiority of belantamab mafodotin/Bd over DAR/Bd.

Table 45. Results of interim analysis for PFS (DREAMM-7 study, ITT population, by independent review committee, data cut-off on October 2, 2023)

	Belantamab mafodotin/Bd	DAR/Bd
Number of subjects	243	251
Number of deaths or progression (%)	91 (37.4)	158 (62.9)
Median [95% CI] (months)	36.6 [28.4, —]	13.4 [11.1, 17.5]
Hazard ratio[*1] [95% CI]	0.41 [0.31, 0.53][*2]	
P-value (one-sided)[*3]	<0.00001	

—, Not estimable; *1, calculated using a Cox proportional hazard model, adjusting for stratification factors: number of prior lines of anti-MM regimens (1 vs. 2 or 3 vs. ≥4), prior BOR therapy (Yes, No), and Revised International Staging System (R-ISS; Stage I vs. II/III); *2, the 96.51% CI corresponding to the level of significance was [0.30, 0.54]; *3, stratified log-rank test (stratification factors the same as those used for the Cox proportional hazard model), level of significance (one-sided), 0.017462

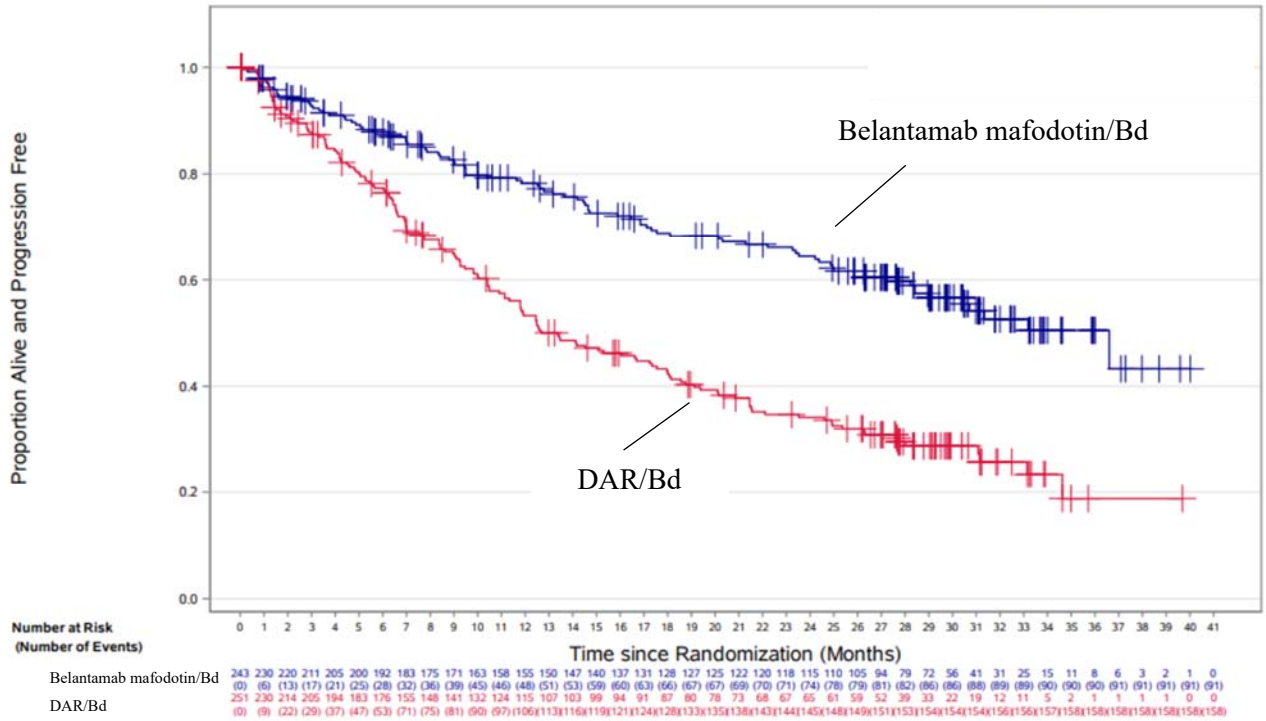

Figure 3. Kaplan-Meier curves for PFS (DREAMM-7 study, ITT population, by independent review committee, data cut-off on October 2, 2023)

During study drug treatment or within 30 days of the last dose, 18 of 242 subjects (7.4%) in the belantamab mafodotin/Bd group and 22 of 246 subjects (8.9%) in the DAR/Bd group died. In addition to disease progression (4 subjects in the DAR/Bd group), other causes of death[41)] were haemorrhage (3 subjects), sepsis (3 subjects), myocardial infarction (1 subject), and unknown (1 subject), and other events (10 subjects[42)]) in the belantamab mafodotin/Bd group; sepsis (2 subjects), haemorrhage (1 subject), cerebrovascular accident (1 subject), and other events (14 subjects[43)]) in the DAR/Bd group. Among these events, a causal relationship to the study drug could not be ruled out for other events (3 subjects[44)]) and haemorrhage (2 subjects) in the belantamab mafodotin/Bd group and other events (2 subjects[45)]) in the DAR/Bd group (no Japanese patients died).

41) In DREAMM-3, DREAMM-7, DREAMM-8, and DREAMM-12 studies, causes of death were reported in the case report form by choosing from the 12 categories shown below. Causes of death included in "other (non-cardiovascular diagnosis)" events and recorded in each case report form (free form field) were to be specified in each footnote field:
"cancer," "cardiac arrhythmia," "haemorrhage," "heart failure," "myocardial infraction," "other cardiovascular diagnosis," "pulmonary embolism (PE)," "sepsis," "stroke," "suicide," "trauma," "other (non-cardiovascular diagnosis)"

42) COVID-19 (2 subjects); late complication of radiotherapy, right bronchopneumonia, lung infection, pneumonia, serious pneumonia, mesenteric vascular thrombosis, acute bilateral polysegmental coronavirus pneumonia, and respiratory failure due to COVID-19 infection (1 subject each)

43) COVID-19 pneumonia (4 subjects); COVID-19 (2 subjects); COVID pneumonia, COVID-19 disease, COVID-19-associated bilateral pneumonia, SARS-COV-2-positive respiratory infection, bilateral pneumonia, acute respiratory failure, respiratory failure, and chest trauma with multiple rib fracture/significant left lung tissue injury and significant metastases to spleen (1 subject each)

44) Right bronchopneumonia, lung infection, and mesenteric vascular thrombosis (1 subject each)

45) COVID-19 pneumonia and SARS-COV-2-positive respiratory infection (1 subject each)

7.1.2.2 Global phase III study (CTD 5.3.5.1-2, 5.3.5.1-3, DREAMM-8 study, main cohort [ongoing since October 2020, data cut-off on January 29, 2024], all Japanese population[46] [ongoing since January 2022, data cut-off on May 27, 2024])

An open-label, randomized study was conducted at 95 study centers in 18 countries and regions including Japan in patients with relapsed or refractory MM[47] (target sample size, 300 subjects[48]) to compare the efficacy and safety of belantamab mafodotin/Pd and VPd. A Japan expansion cohort was established separately from the main cohort of this study to enroll additional Japanese patients. Unless otherwise noted, the results of the main cohort are presented as the results of the DREAMM-8 study. It was planned to evaluate Japanese patients who were enrolled in the main cohort together with those who were enrolled in the Japan expansion cohort. The results for Japanese patients are presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety."

In the belantamab mafodotin/Pd group, in combination with Pd,[49] belantamab mafodotin 2.5 mg/kg was to be administered in Cycle 1 and 1.9 mg/kg in Cycle 2 onward Q4W in 28-day cycles as an intravenous infusion over at least 30 minutes. In the VPd group, VPd[50] was administered in 21-day cycles. In both groups, treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

Subjects who were enrolled in this study and randomized (302 subjects total; 155 subjects in the belantamab mafodotin/Pd group and 147 subjects in the VPd group) were included in the ITT population, which was also the efficacy analysis set (including 3 Japanese subjects in the belantamab mafodotin/Pd group and 6 Japanese subjects in the VPd group). Of the ITT population, 7 subjects who did not receive the study drug (5 subjects in the belantamab mafodotin/Pd group and 2 subjects in the VPd group) were excluded and the remaining 295 subjects (150 subjects in the belantamab mafodotin/Pd group and 145 subjects in the VPd group) were included in the safety analysis set (including 3 Japanese subjects in the belantamab mafodotin/Pd group and 6 Japanese subjects in the VPd group).

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46) The Japanese population enrolled in the main cohort and subjects enrolled in the Japan expansion cohort

47) Patients with ≥1 line of prior anti-MM regimen including LEN were eligible. Patients who had or were intolerant to prior POM therapy, who were intolerant or resistant to BOR, or who had prior anti-BCMA therapy were excluded.

48) The primary endpoint of this study was PFS determined by an independent review committee. Assuming a hazard ratio of 0.60 for belantamab mafodotin/Pd versus VPd (corresponding to median PFS of 20 months and 12 months, respectively) and a one-sided significance level of 2.5%, approximately 173 PFS events provided 90% power to detect a difference between the treatment groups. Considering the duration of follow-up period and other factors, a target sample size of approximately 300 subjects was set.

49) Subjects were to receive POM 4 mg orally on Days 1 to 21, DEX 40 mg (dose may be reduced to 20 mg for patients aged >75 years, who had comorbidities, or were unable to tolerate the starting dose) orally on Days 1, 8, 15, and 22.

50) Subjects were to receive POM 4 mg orally on Days 1 to 14, BOR 1.3 mg/m^2 on Days 1, 4, 8, and 11 (Days 1 and 8 in Cycle 9 onward) subcutaneously, and DEX 20 mg (dose may be reduced to 10 mg for patients aged >75 years, who had comorbidities, or were unable to tolerate the starting dose) orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 in each cycle (Days 1, 2, 8, and 9 in Cycle 9 onward).

The primary endpoint for this study was PFS[51)] determined by an independent review committee according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46). Table 46 shows the main amendment to the statistical analysis plan for this study related to the primary endpoint. The interim analysis (data cut off date, January 29, 2024) added to the Protocol Amendment 4 (dated September 28, 2023) was positioned as the primary analysis.

Table 46. Main changes in statistical analysis plan (DREAMM-8 study)

Protocol	Original version	Amendment 2	Amendment 3	Amendment 4
Date	[redacted]			
Details and reasons for amendment	—	Patient enrollment rate was slower than planned. It was estimated that the prespecified target for PFS events could be achieved with a smaller sample size by extending the follow-up period, and the target sample size was updated accordingly.	The outline of sample size re-estimation provided in the IDMC charter was described in the protocol	Because the US regulatory authorities request for higher than initially planned maturity of OS data at the time the primary PFS results would be obtained, the study period was extended by approximately 6 months. The timing of primary PFS analysis was changed and an interim analysis was added.
Interim analyses and objective	Harm	No change	No change	First: harm Second: efficacy
Time of interim analyses	PFS events: ≈ 35 events (≈ 25%)	No change	No change	First: PFS events: ≈ 35 events (≈ 25%) Second: PFS events: ≈ 145 events (≈ 84%)
Sample size re-estimation	Described to specify the details of sample size re-estimation in the IDMC charter	No change	Sample size re-estimation based on conditional power (*Stat Med.* 2011;30:3267-84). PFS events may be increased up to 163 events.	No change
Time of final analysis	PFS events: 139 events	No change	PFS events: 139 events and at least 6 months of follow-up	PFS events: 173 events
Power	85%	No change	No change	>90%
Target sample size	450 subjects	300 subjects	No change	No change

—, not applicable

Among the changes shown in Table 46, the details of changes to the statistical plan and sample size re-estimation for this study are as follows. The original version of the protocol (dated [redacted], 20[redacted]) specified that sample size re-estimation might be required at the time of the first interim analysis, and the IDMC charter (version 4.0, dated [redacted], 20[redacted]) provided detailed procedures for sample size re-estimation, which allowed the number of PFS events to be increased up to 163. However, based on

51) The PFS was defined as time from randomization to the date of disease progression first recorded by the independent review committee or death from any cause whichever is earlier. Patients who met the following were to be censored at the applicable date.
- Randomization date for patients with no adequate post-baseline assessment before start of new anti-MM pharmacotherapy who had no documented disease progression or had not died.
- Date of last disease assessment for patients with adequate post-baseline assessment who had no documented disease progression or had not died, and started new anti-MM pharmacotherapy
- Randomization date for patients with no post-baseline assessment who had documented disease progression or had died after extended loss-to-follow-up time; or appropriate assessment date for patients with post-baseline assessment.

IDMC evaluation results, IDMC recommended continuation of the study without changing the number of PFS events. Protocol Amendment 4 (dated [redacted], 20[redacted]) was implemented in response to a request by the US regulatory authorities for higher than initially planned maturity of OS data at the time the primary PFS analysis results would be obtained. Because patient enrollment in the study had been completed at the time the feedback from the US regulatory authorities was received, it was necessary to extend the study period to obtain the additional OS events required. Consequently, the study was extended by approximately 6 months. As the timing of the primary analysis for PFS was expected to be delayed, the projected number of PFS events at that time was revised from 139 events (Protocol Amendment 3) to 173 events (Protocol Amendment 4), and the second interim analysis was added. The applicant explained that, based on the simulations using the final study plan following the amendment, the type-I error rate was adequately controlled, confirming that the change in the number of required PFS events was appropriate. The Lan-DeMets approach approximating the O'Brien-Fleming α spending function was to be used to control the type-I error rate associated with the implementation of an interim analysis.

Table 47 shows the primary endpoint, PFS determined by an independent review committee according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46), and Figure 4 shows Kaplan-Meier curves. The results demonstrated the superiority of belantamab mafodotin/Pd over VPd.

Table 47. Results of PFS analysis (DREAMM-8 study, ITT population, by independent review committee, data cut-off on January 29, 2024)

	Belantamab mafodotin/Pd	VPd
Number of subjects	155	147
Number of deaths or progression (%)	62 (40.0)	80 (54.4)
Median [95% CI] (months)	— [20.6, —]	12.7 [9.1, 18.5]
Hazard ratio[*1] [95% CI]	0.52 [0.37, 0.73][*2]	
P-value (one-sided)[*3]	<0.001	

—, Not estimable; *1, calculated using a Cox proportional hazard model, adjusting for stratification factors: number of prior lines of anti-MM regimens (1 vs. 2 or 3 vs. ≥4) and prior BOR therapy (Yes, No); *2, the 97.33% CI corresponding to the level of significance was [0.35, 0.76]; *3, stratified log-rank test (stratification factors the same as those used for the Cox Proportional Hazard Model), level of significance (one-sided), 0.013361

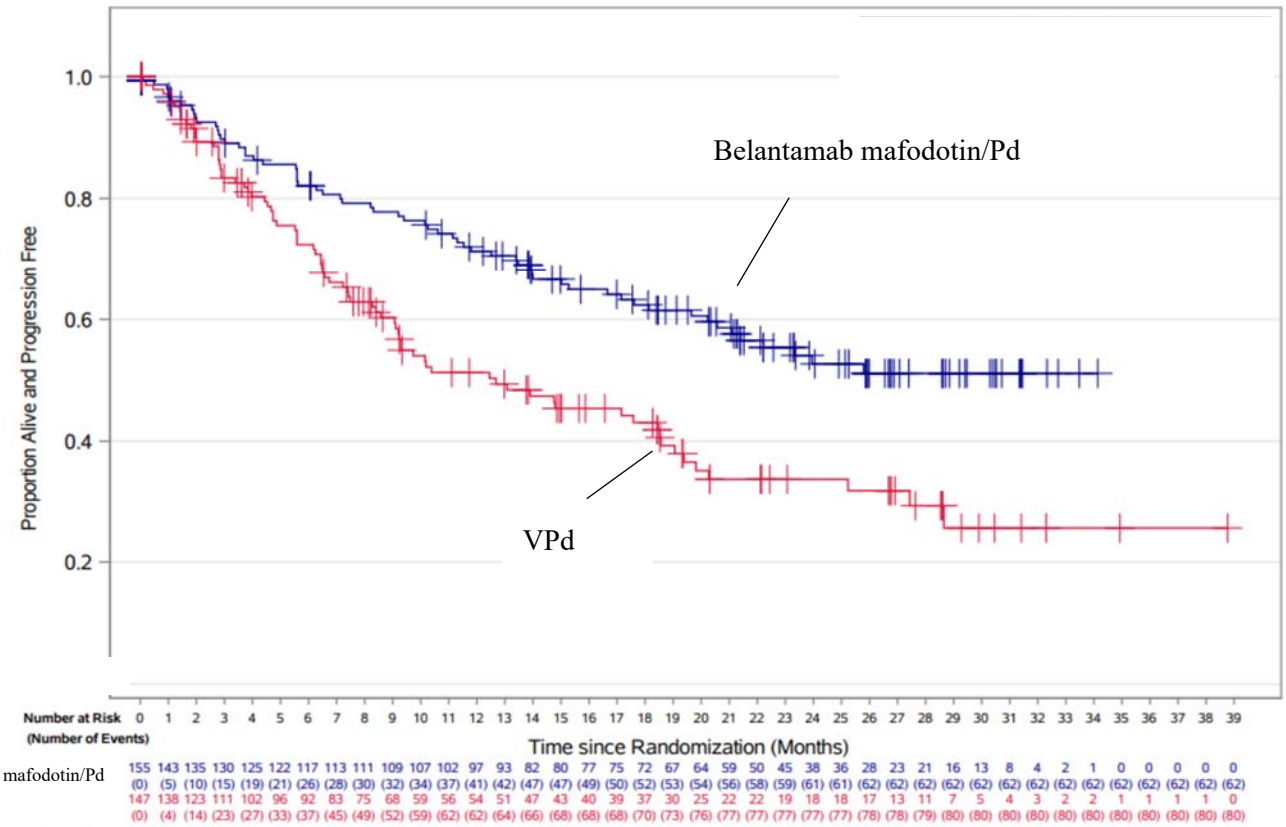

Figure 4. Kaplan-Meier curves for PFS (DREAMM-8 study, ITT population, by independent review committee, data cut-off on January 29, 2024)

During study drug treatment or within 30 days of the last dose, 14 of 150 subjects (9.3%) in the belantamab mafodotin/Pd group and 16 of 145 subjects (11.0%) in the VPd group died. In addition to disease progression (3 subjects in the belantamab mafodotin/Pd group and 4 subjects in the VPd group), other causes of death[41)] were myocardial infarction (1 subject), pulmonary embolism (1 subject), cerebrovascular accident (1 subject), and other events (8 subjects[52)]) in the belantamab mafodotin/Pd group; cerebrovascular accident (1 subject) and other events (11 subjects[53)]) in the VPd group. Among these events, a causal relationship to the study drug could not be ruled out for other events (1 subject[54)]) in the belantamab mafodotin/Pd group (no Japanese patients died).

52) COVID-19 infection (3 subjects); COVID-19, chest pain precordial, death from natural causes, pneumonia, and severe pneumonia (1 subject each)
53) Unknown (2 subjects), pneumonia aspiration, lower respiratory tract infection, acute pulmonary oedema, gram-negative sepsis, sepsis, COVID-19, general physical condition decreased, pneumonia, and cause undetermined (1 subject each)
54) Pneumonia

7.1.2.3 Global phase III study (CTD 5.3.5.1-1, DREAMM-3 study, ongoing since April 2020, data cut-off on September 12, 2022)

An open-label, randomized study was conducted at 108 study centers in 18 countries and regions including Japan in patients with relapsed or refractory MM[55] (target sample size, approximately 320 subjects[56]) to compare the efficacy and safety of belantamab mafodotin monotherapy and Pd.

In the belantamab mafodotin group, belantamab mafodotin 2.5 mg/kg was to be administered intravenously Q3W in 21-day cycles, while in the Pd group, Pd[57] was administered in 28-day cycles. In both groups, treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

Subjects who were enrolled in this study and randomized (325 subjects total; 218 subjects in the belantamab mafodotin group and 107 subjects in the Pd group) were included in the ITT population, all of whom were included in the efficacy analysis set (including 12 Japanese subjects in the belantamab mafodotin group and 5 Japanese subjects in the Pd group). Of the ITT population, 6 subjects who did not receive the study drug (1 subject in the belantamab mafodotin group and 5 subjects in the Pd group) were excluded and the remaining 319 subjects (217 subjects in the belantamab mafodotin group and 102 subjects in the Pd group) were included in the safety analysis set (including 12 Japanese subjects in the belantamab mafodotin group and 5 Japanese subjects in the Pd group).

The primary endpoint for this study was investigator-assessed PFS according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46). No statistically significant improvement in the belantamab mafodotin group was demonstrated compared with the Pd group (hazard ratio [95% CI], 1.03 [0.72, 1.47], stratified Cox proportional hazard model,[58] one-sided level of significance, 0.025).

During study drug treatment or within 30 days of the last dose, 16 of 217 subjects (7.4%) in the belantamab mafodotin group and 13 of 102 subjects (12.7%) in the Pd group died. In addition to disease progression (10 subjects in the belantamab mafodotin group and 3 subjects in the Pd group), other causes of death[41] were sepsis (2 subjects) and other events (4 subjects[59]) in the belantamab mafodotin group; cardiac failure (2 subjects), sepsis (1 subject), other cardiovascular diseases (1 subject[60]), and other

55) Eligible patients were those who had ≥2 prior lines of anti-MM regimens including LEN and proteasome inhibitor.
56) The primary endpoint was investigator-assessed PFS. Assuming a hazard ratio of 0.57 for belantamab mafodotin versus Pd (median PFS: 7 months vs 4 months) and a one-sided significance level of 2.5%, 151 PFS events with a 2:1 randomization ratio (belantamab mafodotin: Pd) provided 90% power to detect a difference between the treatment groups. Considering the duration of follow-up period and other factors, a target sample size of approximately 320 subjects was set.
57) POM 4 mg was to be administered orally on Days 1 to 21, and DEX 40 mg orally on Days 1, 8, 15, and 22 (for patients who were aged >75 years, reduce to 20 mg).
58) Stratification factors: use of anti-CD38 monoclonal antibody drugs, ISS (Stage I/II vs. III), and number of prior lines of anti-MM regimens (≤3 vs. ≥4)
59) Cardio-respiratory arrest, febrile infection, death due to automobile accident, and cardiac arrest
60) Cardiac arrest

events (6 subjects[61]) in the Pd group. Among these events, a causal relationship to the study drug could not be ruled out for other events (1 subject[62]) in the Pd group (no Japanese patients died).

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.3.2-1, 5.3.3.2-2, DREAMM-1 study [July 2014 to August 2019])

An open-label, uncontrolled study was conducted at 9 overseas study centers in patients with relapsed or refractory MM[63] (target sample size, approximately 80 to 95 subjects in total) to evaluate the safety and other aspects of belantamab mafodotin monotherapy.

The study consisted of a dose-escalation part and a dose-expansion part. Belantamab mafodotin was to be administered intravenously Q3W in 21-day cycles at 0.03, 0.06, 0.12, 0.24, 0.48, 0.96, 1.92, 2.50, 3.40, and 4.60 mg/kg in the dose-escalation part, and at 3.40 mg/kg in the dose-expansion part.

All 73 subjects enrolled in this study received belantamab mafodotin and were included in the safety analysis set. In the dose-escalation part, 38 subjects were evaluated for DLTs.

The first cycle in each part was defined as the evaluation period for DLT, and no DLTs were reported.

During study drug treatment or within 30 days of the last dose, 2 of 73 subjects (2.7%) died, with death being due to disease progression in both cases.

7.1.3.2 Foreign phase I/II study (CTD 5.3.5.2-3, DREAMM-6 study, Arm B[64] [ongoing since September 2018, data cut-off on February 28, 2023])

An open-label, uncontrolled study was conducted at 26 overseas study centers in patients with relapsed or refractory MM (target sample size, 107 subjects) to evaluate the safety and efficacy of belantamab mafodotin/Bd.

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61) Sepsis, COVID-19, respiratory infection, COVID-19 infection, pneumonia, and septic shock
62) Sepsis
63) Eligible patients were as follows: in the dose-escalation part, patients with relapsed or refractory MM, in the dose-expansion part, patients with relapsed or refractory MM and patients with lymphoma (diffuse large B-cell lymphoma [DLBCL] or follicular lymphoma [FL]) expressing BCMA. In this report, results of the MM cohort from the dose-escalation part and dose-expansion part are shown.
64) The DREAMM-6 study consisted of Arm A (belantamab mafodotin in combination with Ld) and Arm B (belantamab mafodotin in combination with Bd), and results data from Arm B were submitted as evaluation data for the present application.

Arm B consisted of the dose-escalation part and a dose-expansion part. In 21-day cycles, in the dose-escalation part, belantamab mafodotin 2.5 or 3.4 mg/kg was administered intravenously Q3W in combination with Bd,[65] while in the dose-expansion part, belantamab mafodotin was administered with dosage regimens[66] combining 3 dose levels (1.9, 2.5, and 3.4 mg/kg) and 4 different administration methods in combination with Bd.[65]

All 107 subjects enrolled in Arm B of this study received belantamab mafodotin and were included in the safety analysis set. In the dose-escalation part, 13 subjects were evaluated for DLTs.

In Cycle 1, which was defined as the evaluation period for DLT, no DLTs were reported.

The primary efficacy endpoint for the dose-expansion part, which is the investigator-assessed overall response rate[67] (defined as PR or better) according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46), was 70.1% (75 of 107 subjects).

During study drug treatment or within 30 days of the last dose, 10 of 107 subjects (9.3%) died. In addition to disease progression (7 subjects), other causes of death were worsening of multiorgan failure (1.9 mg/kg Q6W; Stretch method), COVID-19 (2.5 mg/kg Q6W; Step-down stretch method), and hepatic failure (3.4 mg/kg Q3W; Single method) (1 subject each). Among these events, a causal relationship to the study drug could not be ruled out for COVID-19 and hepatic failure (1 subject each).

7.1.3.3 Foreign phase IIb study (CTD 5.3.5.2-1, 5.3.5.2-2, DREAMM-2 study [June 2018 to March 2022])

An open-label, randomized study was conducted at 58 overseas study centers in patients with relapsed or refractory MM[68] (target sample size, 130 subjects) to evaluate the efficacy and safety of belantamab mafodotin monotherapy.

Belantamab mafodotin 2.5 or 3.4 mg/kg was to be administered intravenously Q3W in 21-day cycles. Treatment was to be continued until disease progression or the treatment discontinuation criteria were met.

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[65] Subjects were to receive BOR 1.3 mg/m^2 subcutaneously or intravenously on Days 1, 4, 8, and 11, and DEX 20 mg once daily orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 in each cycle (dose may be reduced for patients aged >75 years, who had a BMI <18.5 kg/m^2, who had previous unacceptable adverse drug reactions associated with glucocorticoid therapy) for a total of 8 cycles.

[66] Belantamab mafodotin was to be administered using one of the following methods (1) through (8):
- On Day 1 of each cycle, (1) 1.9 mg/kg, (2) 2.5 mg/kg, or (3) 3.4 mg/kg (Single method)
- On Days 1 and 8 in each cycle, (4) 1.25 mg/kg on each day, or (5) 1.7 mg/kg on each day (Split method)
- On Day 1 every 2 cycles (i.e., every 6 weeks), (6) 1.9 mg/kg, or (7) 2.5 mg/kg (Stretch method)
- (8) On Day 1 of Cycle 1, 2.5 mg/kg, on Day 1 every 2 cycles, 1.9 mg/kg (Step-down stretch method)

[67] The integrated results for the 8 cohorts, (1) through (8) in the previous footnote. The results for the response rate (VGPR or better) for each cohort were as follows: (1) 33%, (2) 67%, (3) 44%, (4) 54%, (5) 50%, (6) 25%, (7) 50%, and (8) 58%.

[68] Eligible patients were those with ≥3 prior anti-MM regimens including anti-CD38 monoclonal antibody drugs who were resistant to immunomodulators and proteasome inhibitors.

Subjects who were enrolled in this study and randomized (196 subjects total; 97 subjects in the 2.5 mg/kg group and 99 subjects in the 3.4 mg/kg group) were included in the ITT population, which was also the efficacy analysis set. Of the ITT population, 193 subjects (95 subjects in the 2.5 mg/kg group and 98 subjects in the 3.4 mg/kg group) received at least 1 dose of belantamab mafodotin (frozen liquid) and were included in the safety analysis set.

In this study, belantamab mafodotin 3.4 mg/kg (lyophilized powder) Q3W was administered in a separate cohort, and 25 subjects enrolled were included in the ITT population, which was also the efficacy analysis set. Of the ITT population, 24 subjects who received belantamab mafodotin (lyophilized powder) were included in the safety analysis set.[69)]

The primary efficacy endpoint, independent review committee-assessed overall response rate (defined as PR or better) according to the IMWG criteria (*Lancet Oncol.* 2016;17:e328-46), was 32.0% (31 of 97 subjects) in the 2.5 mg/kg group (frozen liquid), 35.4% (35 of 99 subjects) in the 3.4 mg/kg group (frozen liquid), and 52.0% (13 of 25 subjects) in the 3.4 mg/kg group (lyophilized powder).

During study drug treatment or within 30 days of the last dose, 8 of 95 subjects (8.4%) in the 2.5 mg/kg group (frozen liquid), 16 of 99 subjects[70)] (16.2%) in the 3.4 mg/kg group (frozen liquid), and 2 of 24 subjects (8.3%) in the 3.4 mg/kg group (lyophilized powder) died. In addition to disease progression (6 subjects in the 2.5 mg/kg group [frozen liquid], 8 subjects in the 3.4 mg/kg group [frozen liquid], and 2 subjects in the 3.4 mg/kg group [lyophilized powder]), other causes of death were myocardial infarction and sepsis (1 subject each) in the 2.5 mg/kg group (frozen liquid); sepsis (2 subjects); hematoma compressing the brain stem due to central brain herniation caused by obstructive hydrocephalus and clotting disorder derived from thrombocytopenia secondary to multiple myeloma (1 subject), haemorrhage (1 subject), cardiac failure (1 subject), respiratory infection (1 subject), cerebral haemorrhage (1 subject), and macrophage activation syndrome (1 subject) in the 3.4 mg/kg group (frozen liquid). Among these events, a causal relationship to the study drug could not be ruled out for sepsis (1 subject) in the 2.5 mg/kg group (frozen liquid), cerebral haemorrhage and macrophage activation syndrome (1 subject each) in the 3.4 mg/kg group (frozen liquid).

69) Of the 25 subjects enrolled in the 3.4 mg/kg group (lyophilized powder), 1 subject did not receive the lyophilized powder formulation, but instead received the frozen liquid formulation. The safety of this subject was therefore evaluated as a member of the 3.4 mg/kg group (frozen liquid).

70) Including 1 subject who was enrolled in the 3.4 mg/kg group (lyophilized powder) but did not receive the lyophilized powder formulation but instead received the frozen liquid formulation.

7.2 Reference data

7.2.1 Foreign studies

7.2.1.1 Foreign phase I study (CTD 5.3.3.3-1, DREAMM-12 study, Part 1 [ongoing since October 2020, data cut-off on September 15, 2022])

An open-label, uncontrolled study was conducted at 25 overseas study centers in patients with relapsed or refractory MM and renal impairment[71)] (target sample size, up to 36 subjects) to evaluate the safety and other aspects of belantamab mafodotin.

All 23 subjects enrolled in the study received belantamab mafodotin and were included in the safety analysis set.

During study drug treatment or within 30 days of the last dose, 2 of 23 subjects (8.7%) died. One of the subjects died due to disease progression, and the other subject died[41)] due to other events.[72)] A causal relationship to the study drug was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA plans to conduct an efficacy and safety review of belantamab mafodotin/Bd and belantamab mafodotin/Pd in patients with relapsed or refractory MM focusing primarily on the results from the DREAMM-7 and DREAMM-8 studies. Efficacy and safety in Japanese patients will be evaluated in a systematic manner based on the DREAMM-7, DREAMM-8, and other studies in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), "Partial Amendment to Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice, dated December 10, 2021), "General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1, dated June 12, 2018), and other guidelines. Results data from the DREAMM-3 study, which evaluated belantamab mafodotin monotherapy, will be used for the safety evaluation.

7.R.2 Efficacy

Based on the following discussions, PMDA concluded that belantamab mafodotin/Bd and belantamab mafodotin/Pd have efficacy in the treatment of patients with relapsed or refractory MM.

7.R.2.1 Control group

The applicant's explanation about the rationale for the selection of control in the DREAMM-7 and DREAMM-8 studies:

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71) Part 1 evaluated patients with normal renal function or mild impairment (iGFR: ≥60 mL/min) or severe (iGFR: 15 to 29 mL/min) and Part 2 evaluated patients with end-stage renal disease. Part 2 is ongoing. Results data from Part 1 were submitted for the present application.

72) Intestinal ischaemia

At the time the DREAMM-7 study (2019-2020) was designed, DAR/Bd was recommended as a treatment option for the patient population of the DREAMM-7 study in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma (NCCN Guidelines) (v.3.2018), European Society of Medical Oncology (ESMO) Guidelines (*Ann Oncol.* 2017;28:iv52-61), and Practical Guidelines for Hematological Malignancies 2018 revised edition (Japanese Society of Hematology). Therefore, DAR/Bd was established as the control group in DREAMM-7.

At the time the DREAMM-8 study (2019-2020) was designed, VPd was recommended as a treatment option for patients with relapsed or refractory MM in the NCCN Guidelines (v.3.2018), ESMO Guidelines (*Ann Oncol.* 2017;28:iv52-61), and Practical Guidelines for Hematological Malignancies 2018 revised edition (Japanese Society of Hematology). In particular, because efficacy of POM, another immunomodulator similar to LEN, for patients resistant to LEN was reported (*Lancet Oncol*. 2019;20:781-94), VPd, a regimen that includes POM, was expected to be effective. Therefore, VPd was established as the control group in the DREAMM-8 study, which was conducted in patients with at least 1 prior anti-MM regimen including LEN.

PMDA accepted the applicant's explanation.

7.R.2.2 Efficacy endpoints

The applicant's explanation about the efficacy endpoints in the DREAMM-7 and DREAMM-8 studies:
Multiple myeloma is a refractory disease characterized by successive relapses, and achieving a cure remains difficult with currently available treatments. In patients with relapsed or refractory MM, improvement of PFS is expected to slow disease progression and delay the time to the next treatment (*Leukemia*. 2006;20:1467-73), which is clinically meaningful. Therefore, PFS was selected as the primary endpoint for the DREAMM-7 and DREAMM-8 studies.

PMDA's view:
The applicant's explanation is generally acceptable. However, to evaluate the efficacy of belantamab mafodotin/Bd and belantamab mafodotin/Pd, the results for OS, established as a secondary endpoint, are also important. Accordingly, it was decided that the efficacy of belantamab mafodotin/Bd and belantamab mafodotin/Pd will be evaluated primarily based on the primary endpoint, PFS determined by an independent review committee according to the IMWG criteria, as well as OS.

7.R.2.3 Results of efficacy evaluation

The applicant's explanation about the efficacy evaluation results of the DREAMM-7 and DREAMM-8 studies:
(1) DREAMM-7 study
The analysis of PFS determined by an independent review committee according to the IMWG criteria (primary endpoint) demonstrated the superiority of belantamab mafodotin/Bd over DAR/Bd [see Section 7.1.2.1]. In the DREAMM-7 study, the statistical analysis plan for efficacy was amended after

the start of the study (Table 44). In the initial plan, the Haybittle-Peto method was to be used for interim analyses to control the type-I error rate of the overall study, with a constant, extremely low level of significance regardless of timing or number of interim analyses. However, to allow evaluation of efficacy with more mature data and facilitate consideration of early stopping due to efficacy when PFS clearly favors the treatment, the original method was changed to the Lan-DeMets approach that approximates the O'Brien-Fleming α spending function. Because this change was made without referring to the results of the ongoing DREAMM-7 study, it will not affect the interpretation of the results. It is considered that there is no increase in type-I error rate.

If the superiority of belantamab mafodotin/Bd over DAR/Bd is demonstrated based on the primary endpoint, hierarchical hypothesis testing was to be performed for overall survival (OS) and duration of response, which are secondary endpoints. To control the type-I error rate associated with the interim analyses for OS, the Lan-DeMets O'Brien-Fleming α spending function was to be used.

Table 48 shows the interim analysis results for OS[73)] and Figure 5 shows the Kaplan-Meier curves.

Table 48. Interim analysis results for OS (DREAMM-7 study, ITT population, data cut-off on October 2, 2023)

	Belantamab mafodotin/Bd	DAR/Bd
Number of subjects	243	251
Number of deaths (%)	54 (22.2)	87 (34.7)
Median [95% CI] (months)	— [—, —]	— [—, —]
Hazard ratio*1 [95% CI]	0.57 [0.40, 0.80]	
P-value (one-sided)*2	0.00049	

—, Not estimable; *1, calculated using a Cox proportional hazard model, adjusting for stratification factors: number of prior lines of anti-MM regimens (1 vs. 2 or 3 vs. ≥4), prior BOR therapy (Yes, No), and R-ISS (Stage I vs. II/III); *2, stratified log-rank test (stratification factors the same as those used for the Cox proportional hazard model), level of significance (one-sided), 0.00038

73) The OS analysis was planned to include 3 interim analyses (at the time of the interim PFS analysis; at the time of the final PFS analysis or upon the occurrence of approximately 178 OS events; and upon the occurrence of approximately 266 OS events), and the final analysis (upon occurrence of 355 OS events). This analysis corresponds to the results at the time of the interim PFS analysis.

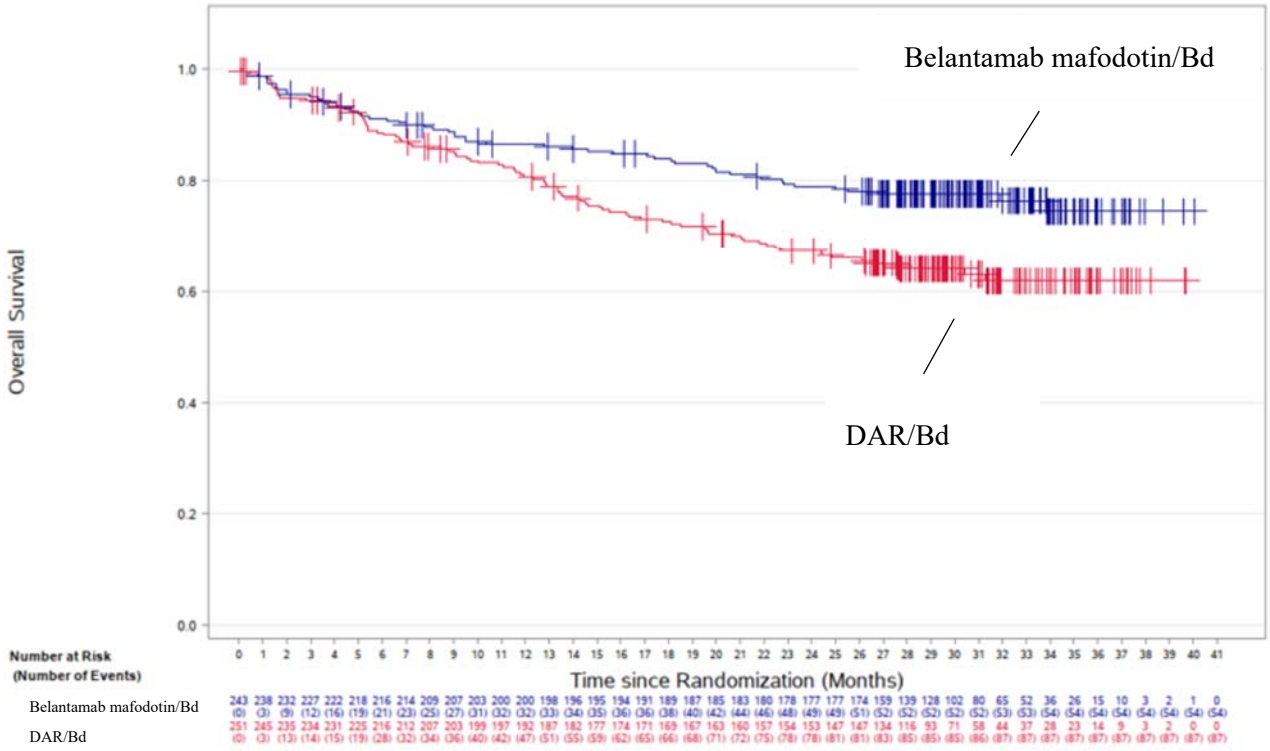

Figure 5. Kaplan-Meier curves for OS (DREAMM-7 study, ITT population, data cut-off on October 2, 2023)

(2) DREAMM-8 study

The analysis of PFS determined by an independent review committee according to the IMWG criteria (primary endpoint) demonstrated the superiority of belantamab mafodotin/Pd over VPd [see Section 7.1.2.2]. If the superiority of belantamab mafodotin/Pd over VPd is demonstrated based on the primary endpoint, hierarchical hypothesis testing was to be performed for OS, the secondary endpoint. To control the type-I error rate associated with the interim analyses for OS, the Lan-DeMets O'Brien-Fleming α spending function was to be used.

Table 49 shows the analysis results for OS[74)] and Figure 6 shows the Kaplan-Meier curves.

Table 49. Analysis results for OS (DREAMM-8 study, ITT population, data cut-off on January 29, 2024)

	Belantamab mafodotin/Pd	VPd
Number of subjects	155	147
Number of deaths (%)	49 (31.6)	56 (38.1)
Median [95% CI] (months)	— [33.0, —]	— [25.2, —]
Hazard ratio*1 [95% CI]	0.77 [0.53, 1.14]	
P-value (one-sided)*2	0.095	

—, Not estimable; *1, calculated using a Cox proportional hazard model, adjusting for stratification factors: number of prior lines of anti-MM regimens (1 vs. 2 or 3 vs. ≥4) and prior BOR therapy (Yes, No); *2, stratified log-rank test (stratification factors the same as those used for the Cox proportional hazard model), level of significance (one-sided), 0.0013

74) The OS analysis was planned to include 3 interim analyses (at the time of the interim PFS analysis; at the time of final PFS analysis or upon the occurrence of approximately 130 OS events; and upon the occurrence of approximately 163 OS events), and the final analysis (upon the occurrence of 217 OS events). This analysis corresponds to the results at the time of the interim PFS analysis.

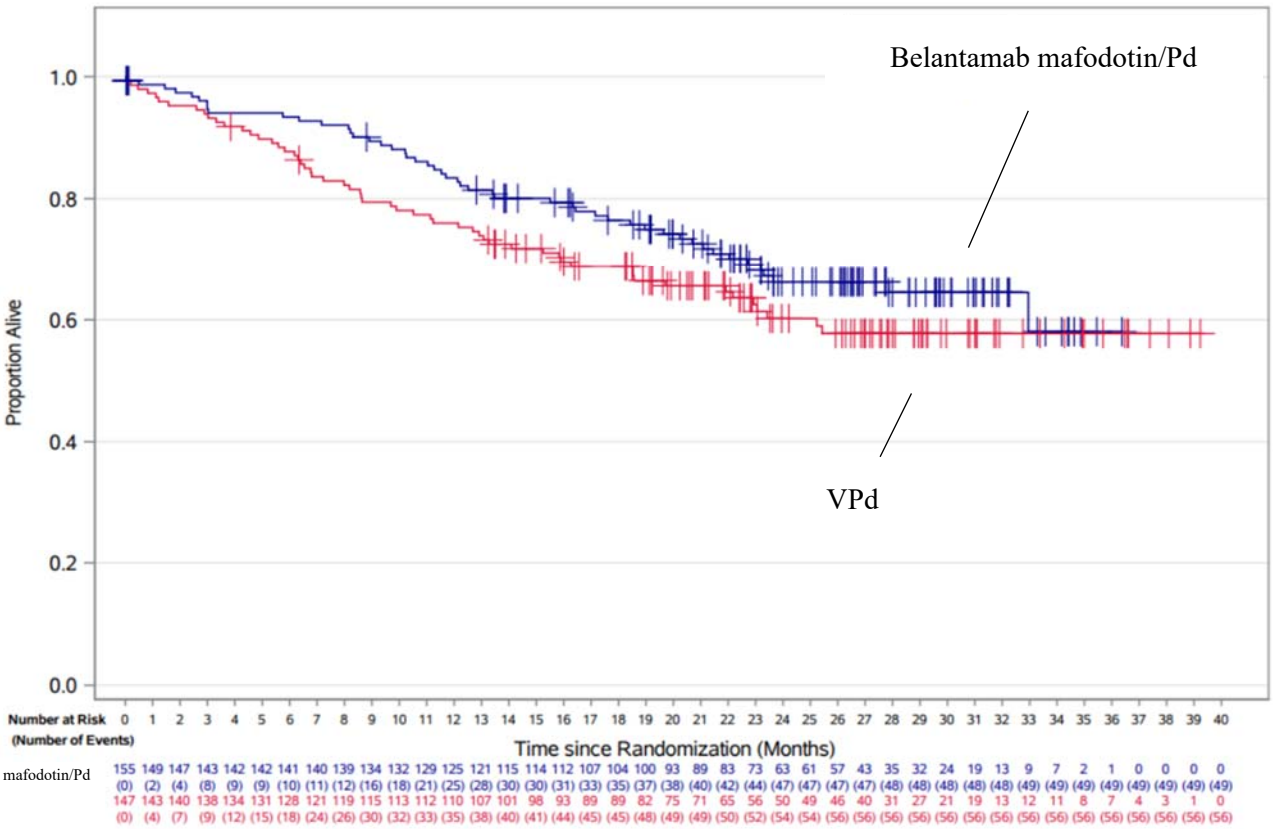

Figure 6. Kaplan-Meier curves for OS (DREAMM-8 study, ITT population, data cut-off on January 29, 2024)

PMDA's view:

Based on the following factors, the efficacy of belantamab mafodotin/Bd and belantamab mafodotin/Pd in the treatment of patients with relapsed or refractory MM was demonstrated.

- Based on the PFS determined by an independent review committee according to the IMWG criteria, the primary endpoint of the DREAMM-7 and DREAMM-8 studies, both belantamab mafodotin/Bd and belantamab mafodotin/Pd were superior to the respective control and the obtained results are clinically meaningful.
- In the DREAMM-7 and DREAMM-8 studies, neither belantamab mafodotin/Bd nor belantamab mafodotin/Pd showed a trend towards decreasing OS compared with the respective control.

7.R.2.4 Efficacy in Japanese patients

The applicant's explanation about efficacy in Japanese patients in the DREAMM-7 and DREAMM-8 studies:

(1) DREAMM-7 study

When participation of Japanese patients in the DREAMM-7 study was decided, the remaining patient enrollment period was limited. Accordingly, the Japan expansion cohort was established separately and enrollment in this cohort remained open after recruitment for the main cohort had closed. The Japan expansion cohort evaluated the efficacy of belantamab mafodotin/Bd in Japanese patients (as a result, 2

Japanese patients,[75] both of whom were in the belantamab mafodotin/Bd group, were enrolled in the main cohort). The efficacy results in the Japan expansion cohort,[76] PFS as determined by an independent review committee according to the IMWG criteria (primary endpoint), are shown in Table 50 and Kaplan-Meier curves are presented in Figure 7.

Table 50. PFS analysis results in the Japan expansion cohort (DREAMM-7 study, ITT population, by independent review committee, data cut-off on April 3, 2024)

	Belantamab mafodotin/Bd	DAR/Bd
Number of subjects	10	14
Number of deaths or progression (%)	3 (30.0)	8 (57.1)
Median [95% CI] (months)	— [7.0, —]	11.1 [4.9, —]
Hazard ratio*1 [95% CI]	0.40 [0.11, 1.52]	

—, Not estimable; *1, calculated using the unstratified Cox proportional hazard model

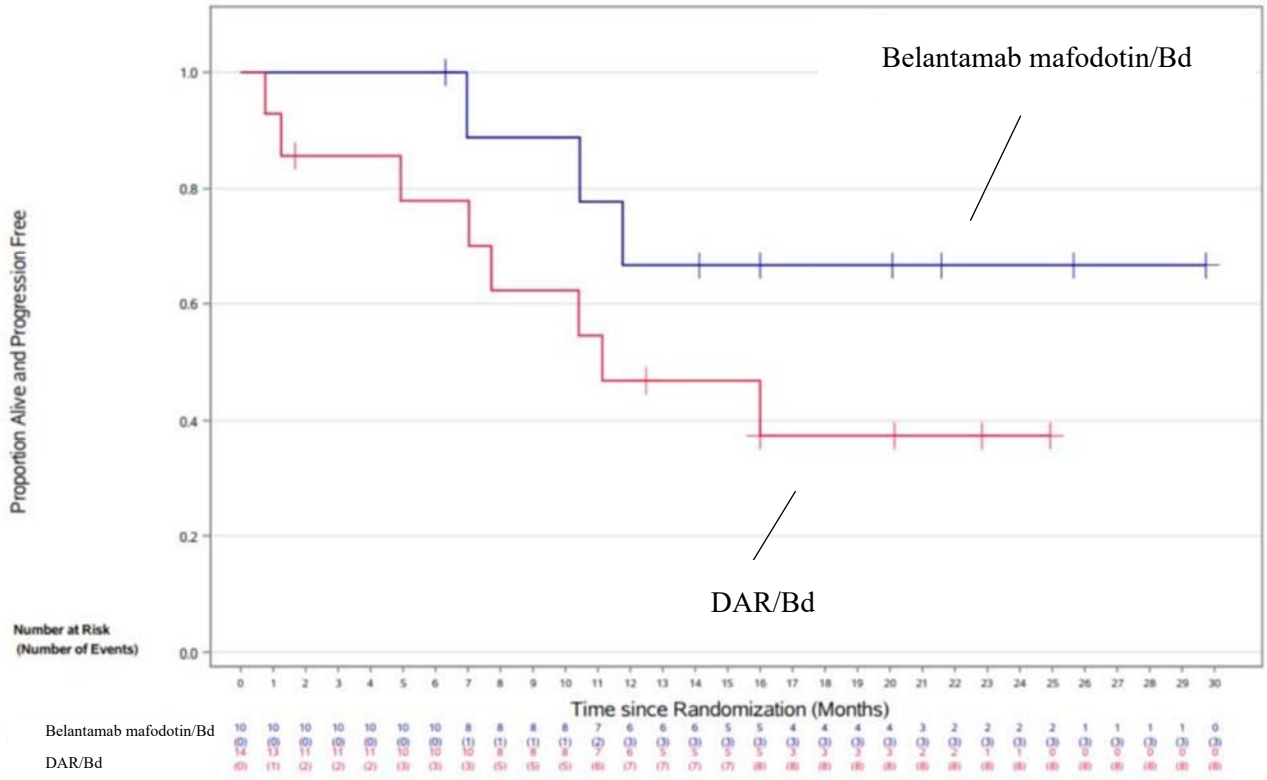

Figure 7. Kaplan-Meier curves for PFS in the Japan expansion cohort (DREAMM-7 study, ITT population, by independent review committee, data cut-off on April 3, 2024)

(2) DREAMM-8 study

Since the number of Japanese patients enrolled in the main cohort remained at 8, which did not meet the planned target of 20 subjects, a separate cohort was established and enrollment in this Japan expansion cohort continued after recruitment in the main cohort had closed. Efficacy in Japanese patients in the DREAMM-8 study was evaluated based on the results of the main cohort (9 Japanese subjects total, 3

[75] At the data cut-off date for the overall population (October 2, 2023), the follow-up period in these 2 subjects was 26.28 months and 26.35 months, and study drug treatment was ongoing. The efficacy results showed that the best overall response as determined by an independent review committee was stringent complete response (sCR) for both subjects. No PFS events occurred in these 2 subjects, with a duration of response of 25.56 months for both (censored by data cut-off).

[76] The protocol specified that in the Japan expansion cohort of the DREAMM-7 study, upon occurrence of 14 PFS events, data should be cut off. However, because favorable results were obtained in the main cohort, data were cut off after the occurrence of 11 PFS events.

subjects in the belantamab mafodotin/Pd group and 6 subjects in the VPd group), and in the Japan-specific supplemental analyses of the all Japanese population (21 subjects), which integrated the results from the Japan expansion cohort (12 subjects) in addition to those from the main cohort.

Table 51 shows the PFS analysis results of the Japanese population in the main cohort (9 subjects total; 3 subjects in the belantamab mafodotin/Pd group and 6 subjects in the VPd group), and Figure 8 shows the Kaplan-Meier curves.

Table 51. Results of PFS analysis in Japanese population in the main cohort (DREAMM-8 study, ITT population, by independent review committee, data cut-off on January 29, 2024)

	Belantamab mafodotin/Pd	VPd
Number of subjects	3	6
Number of deaths or progression (%)	1 (33.3)	2 (33.3)
Median [95% CI] (months)	— [4.0, —]	18.5 [14.8, —]
Hazard ratio*1 [95% CI]	0.88 [0.08, 10.26]	

—, Not estimable; *1, calculated using the unstratified Cox proportional hazard model

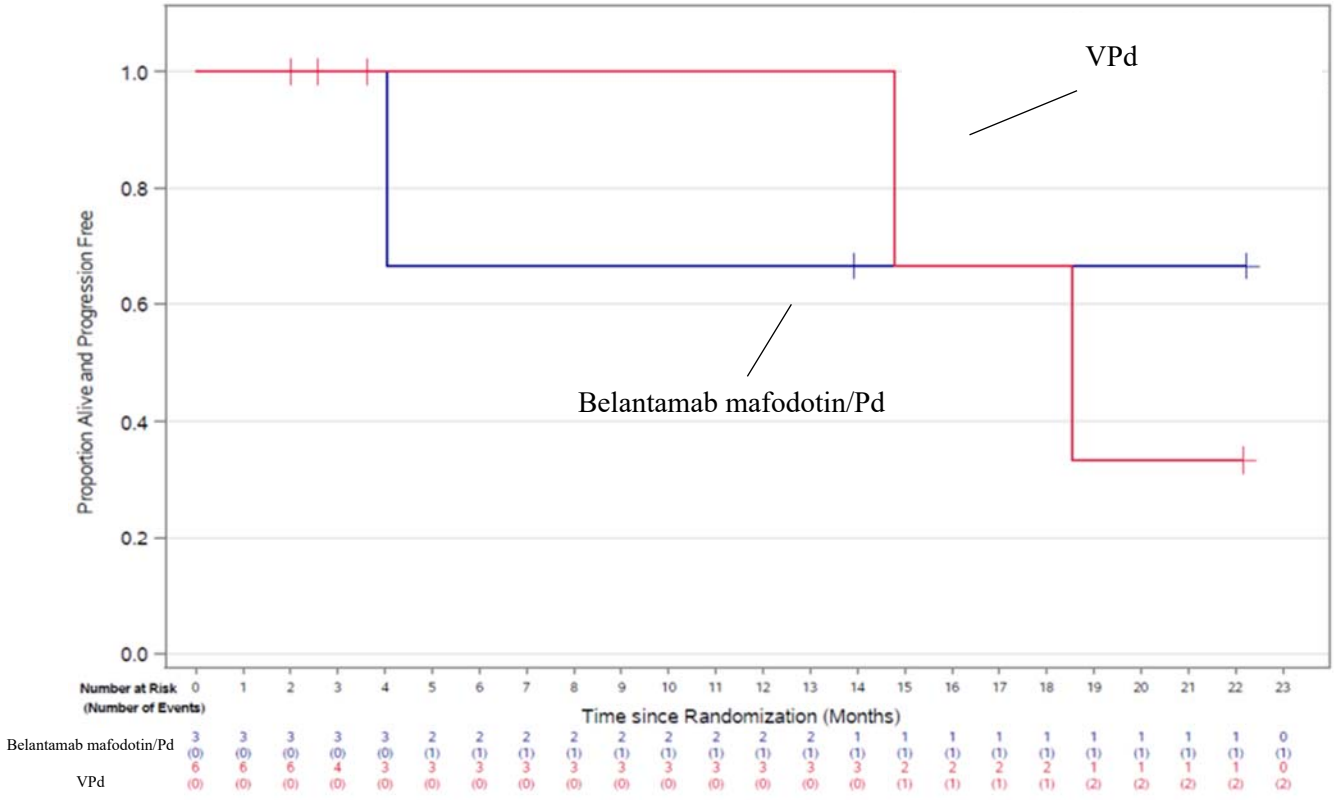

Figure 8. Kaplan-Meier curves for PFS in the Japanese population in the main cohort (DREAMM-8 study, ITT population, data cut-off on January 29, 2024)

Table 52 shows the PFS analysis results for the all Japanese population (21 subjects total; 10 subjects in the belantamab mafodotin/Pd group and 11 subjects in the Vpd group) and Figure 9 shows the Kaplan-Meier curves.

Table 52. Results of PFS analysis in the all Japanese population (DREAMM-8 study, ITT population, by independent review committee, data cut-off on May 27, 2024)

	Belantamab mafodotin/Pd	VPd
Number of subjects	10	11
Number of deaths or progression (%)	2 (20.0)	5 (45.5)
Median [95% CI] (months)	— [0.2, —]	14.8 [1.9, —]
Hazard ratio*1 [95% CI]	0.53 [0.10, 2.78]	

—, Not estimable; *1, calculated using the unstratified Cox proportional hazard model

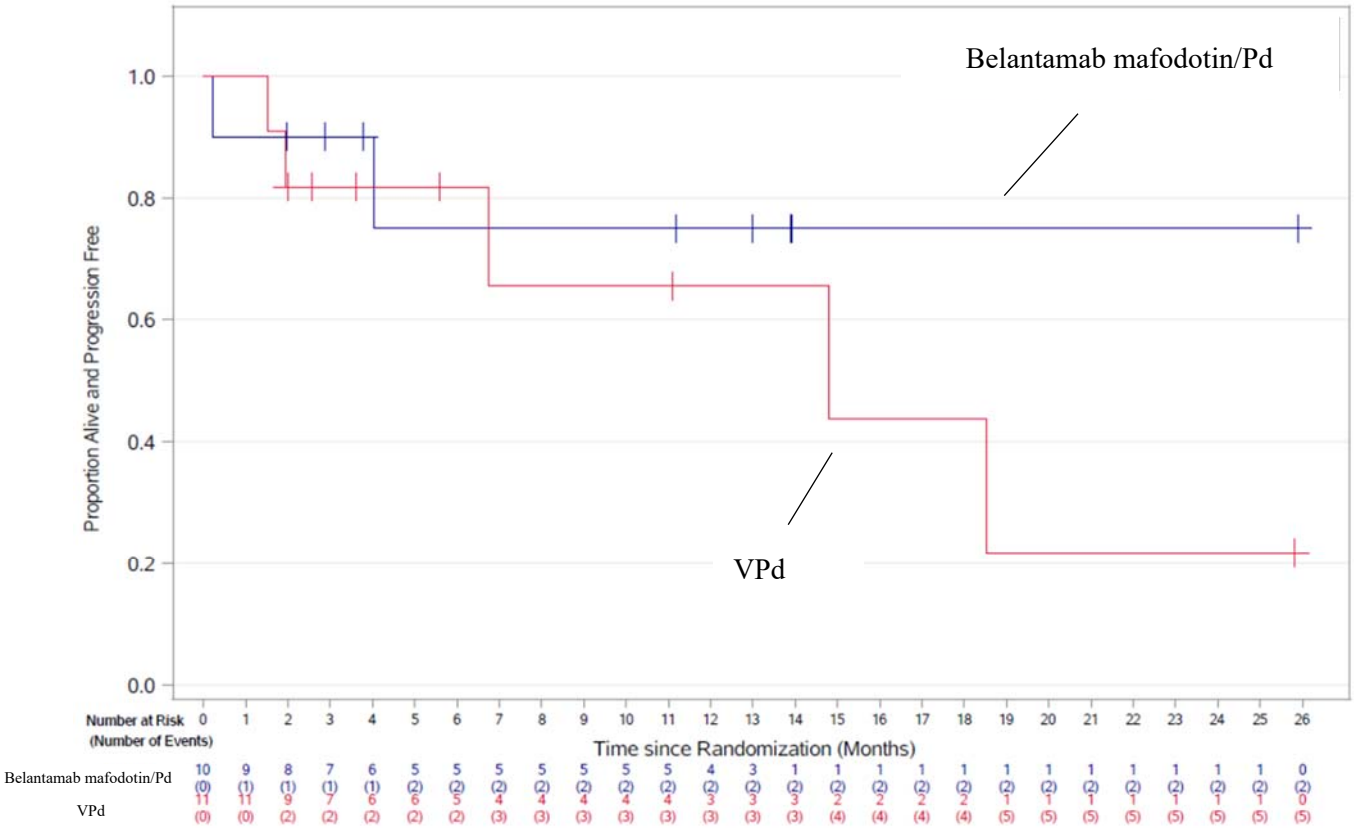

Figure 9. Kaplan-Meier curves for PFS in the all Japanese population (DREAMM-8 study, ITT population, data cut-off on May 27, 2024)

PMDA's view:

Only a small number of Japanese patients were enrolled in the main cohort of the DREAMM-7 and DREAMM-8 study. Furthermore, in both studies, the Japan expansion cohort differs from the main cohort, and the follow-up period was of limited duration. While these factors make appropriate evaluation of consistency with the overall population difficult, the efficacy of belantamab mafodotin/Bd and belantamab mafodotin/Pd in Japanese patients is considered to be promising based on the following points.

- In both studies, there were no trends in the PFS (primary endpoint) results in the Japanese population that are clearly different from those in the overall population.
- No clear differences have been identified between Japanese and non-Japanese populations in terms of diagnosis and treatment of relapsed or refractory MM and the PK of belantamab mafodotin [see Section 6.2.7].

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

Based on the discussions in the following sections, PMDA considered that adverse events that require particular attention when belantamab mafodotin/Bd or belantamab mafodotin/Pd is used are eye disorders, cytopenia, infections, gastrointestinal disorders, bleeding, infusion reaction, interstitial lung disease (ILD), and second primary malignancies. Patients should be carefully monitored for these events when belantamab mafodotin is used.

Although the use of belantamab mafodotin requires particular caution due to the risk of the adverse events described above, PMDA concluded that patients should be able to tolerate belantamab mafodotin/Bd and belantamab mafodotin/Pd provided that appropriate steps, such as monitoring and management of adverse events, are taken by a physician with sufficient knowledge and experience in hematopoietic malignancy treatment, in collaboration with an ophthalmologist.

7.R.3.1 Safety profiles and differences in safety between Japanese and non-Japanese populations

The applicant's explanation about the safety profiles of belantamab mafodotin/Bd and belantamab mafodotin/Pd based on the safety data from the DREAMM-7 and DREAMM-8 studies:

(1) DREAMM-7 study

Table 53 summarizes the safety data from the DREAMM-7 study.

Table 53. Summary of safety data (DREAMM-7 study)

	Number of subjects (%)	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246
All adverse events	242 (100)	246 (100)
Grade ≥3 adverse events	230 (95.0)	192 (78.0)
Adverse events leading to death	23 (9.5)	19 (7.7)
Serious adverse events	121 (50.0)	90 (36.6)
Adverse events leading to treatment discontinuation*1 of the study drug	75 (31.0)	46 (18.7)
Adverse events leading to dose interruption*2 of the study drug	228 (94.2)	185 (75.2)
Adverse events leading to dose reduction*3 of the study drug	182 (75.2)	146 (59.3)

*1, Treatment discontinuation of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX; *2, dose interruption of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX; *3, dose reduction of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX (dose reduction criteria for DAR were not established)

Table 54 shows the adverse events occurring at specified incidences or higher in the belantamab mafodotin/Bd group in the DREAMM-7 study.

Table 54. Adverse events occurring at specified incidences or higher* in the belantamab mafodotin/Bd group (DREAMM-7 study)

PT (MedDRA ver.26.0)	Number of subjects (%)	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246
Adverse events of any grade		
Thrombocytopenia	167 (69.0)	122 (49.6)
Vision blurred	160 (66.1)	26 (10.6)
Dry eye	123 (50.8)	17 (6.9)
Photophobia	114 (47.1)	6 (2.4)
Foreign body sensation in eyes	106 (43.8)	10 (4.1)
Eye irritation	103 (42.6)	13 (5.3)
Diarrhoea	78 (32.2)	77 (31.3)
Eye pain	77 (31.8)	8 (3.3)
Grade ≥3 adverse events		
Thrombocytopenia	134 (55.4)	87 (35.4)
Vision blurred	53 (21.9)	2 (0.8)
Platelet count decreased	44 (18.2)	26 (10.6)
Neutropenia	30 (12.4)	15 (6.1)
Pneumonia	28 (11.6)	10 (4.1)
Adverse events leading to death		
Pneumonia	7 (2.9)	2 (0.8)
COVID-19	3 (1.2)	5 (2.0)
Sepsis	3 (1.2)	3 (1.2)
Serious adverse events		
Pneumonia	27 (11.2)	10 (4.1)
Pyrexia	12 (5.0)	9 (3.7)
Adverse events leading to treatment discontinuation of any study drug		
Peripheral sensory neuropathy	13 (5.4)	6 (2.4)
Adverse events leading to dose interruption of any study drug		
Thrombocytopenia	85 (35.1)	50 (20.3)
Vision blurred	80 (33.1)	1 (0.4)
COVID-19	37 (15.3)	27 (11.0)
Dry eye	33 (13.6)	0
Photophobia	33 (13.6)	0
Eye irritation	32 (13.2)	0
Foreign body sensation in eyes	30 (12.4)	0
Platelet count decreased	28 (11.6)	13 (5.3)
Upper respiratory tract infection	27 (11.2)	25 (10.2)
Peripheral sensory neuropathy	25 (10.3)	15 (6.1)
Eye pain	25 (10.3)	1 (0.4)
Adverse events leading to dose reduction of any study drug		
Thrombocytopenia	67 (22.7)	24 (9.8)
Peripheral sensory neuropathy	33 (13.6)	31 (12.6)
Vision blurred	27 (11.2)	2 (0.8)

*, Adverse events with the following incidence or higher are shown: ≥30% for "adverse events of any grade"; ≥1% for "adverse events leading to death"; ≥10% for "adverse events leading to dose interruption of the study drug"; ≥10% for "Grade ≥3 adverse events"; ≥10% for "adverse events leading to dose reduction of the study drug"; ≥5% for the rest of the categories.

(2) DREAMM-8 study

Table 55 summarizes the safety data from the DREAMM-8 study.

Table 55. Summary of safety data (DREAMM-8 study)

	Number of subjects (%)	
	Belantamab mafodotin/Pd N = 150	VPd N = 145
All adverse events	149 (99.3)	139 (95.9)
Grade ≥3 adverse events	141 (94.0)	110 (75.9)
Adverse events leading to death	17 (11.3)	16 (11.0)
Serious adverse events	95 (63.3)	65 (44.8)
Adverse events leading to treatment discontinuation*1 of the study drug	22 (14.7)	18 (12.4)
Adverse events leading to dose interruption*2 of the study drug	136 (90.7)	109 (75.2)
Adverse events leading to dose reduction*3 of the study drug	92 (61.3)	88 (60.7)

*1, Treatment discontinuation of one or more of the following: belantamab mafodotin, POM, BOR, or DEX; *2, dose interruption of one or more of the following: belantamab mafodotin, POM, BOR, or DEX; *3, dose reduction of one or more of the following: belantamab mafodotin, POM, BOR, or DEX

Table 56 shows the adverse events occurring at specified incidences or higher in the belantamab mafodotin/Pd group in the DREAMM-8 study.

Table 56. Adverse events occurring at specified incidences or higher* in the belantamab mafodotin/Pd group (DREAMM-8 study)

PT (MedDRA ver.26.1)	Number of subjects (%)	
	Belantamab mafodotin/Pd N = 150	VPd N = 145
Adverse events of any grade		
Vision blurred	119 (79.3)	22 (15.2)
Dry eye	91 (60.7)	14 (9.7)
Foreign body sensation in eyes	91 (60.7)	9 (6.2)
Eye irritation	75 (50.0)	13 (9.0)
Neutropenia	72 (48.0)	50 (34.5)
Photophobia	66 (44.0)	6 (4.1)
COVID-19	56 (37.3)	31 (21.4)
Thrombocytopenia	54 (36.0)	44 (30.3)
Eye pain	49 (32.7)	7 (4.8)
Grade ≥3 adverse events		
Neutropenia	63 (42.0)	41 (28.3)
Thrombocytopenia	36 (24.0)	29 (20.0)
Neutrophil count decreased	31 (20.7)	18 (12.4)
Pneumonia	26 (17.3)	11 (7.6)
Vision blurred	26 (17.3)	0
Platelet count decreased	22 (14.7)	18 (12.4)
Visual acuity reduced	20 (13.3)	1 (0.7)
COVID-19 pneumonia	16 (10.7)	6 (4.1)
Visual impairment	15 (10.0)	1 (0.7)
Anaemia	15 (10.0)	19 (13.1)
Adverse events leading to death		
COVID-19 pneumonia	5 (3.3)	2 (1.4)
COVID-19	2 (1.3)	2 (1.4)
Pneumonia	2 (1.3)	1 (0.7)
Serious adverse events		
Pneumonia	27 (18.0)	11 (7.6)
COVID-19 pneumonia	17 (11.3)	6 (4.1)
COVID-19	10 (6.7)	4 (2.8)
Neutropenia	9 (6.0)	4 (2.8)
Adverse events leading to dose interruption of any study drug		
Vision blurred	55 (36.7)	0
COVID-19	42 (28.0)	22 (15.2)
Neutropenia	35 (23.3)	13 (9.0)
Dry eye	32 (21.3)	0
Visual acuity reduced	26 (17.3)	0

PT (MedDRA ver.26.1)	Number of subjects (%)	
	Belantamab mafodotin/Pd N = 150	VPd N = 145
Pneumonia	25 (16.7)	12 (8.3)
Foreign body sensation in eyes	25 (16.7)	0
Eye irritation	24 (16.0)	1 (0.7)
Photophobia	22 (14.7)	0
Upper respiratory tract infection	20 (13.3)	20 (13.8)
Eye pain	19 (12.7)	0
Neutrophil count decreased	15 (10.0)	8 (5.5)
Visual impairment	15 (10.0)	0
Adverse events leading to dose reduction of any study drug		
Neutropenia	21 (14.0)	6 (4.1)
Neutrophil count decreased	15 (10.0)	5 (3.4)

*, Adverse events with the following incidence or higher are shown: ≥30% for "adverse events of any grade"; ≥1% for "adverse events leading to death"; ≥10% for "adverse events leading to dose interruption of the study drug"; ≥10% for "Grade ≥3 adverse events"; ≥10% for "adverse events leading to dose reduction of the study drug"; ≥5% for the rest of the categories. No adverse events with an incidence of ≥5% led to treatment discontinuation of any study drug.

The applicant's explanation about the differences in the safety of belantamab mafodotin/Bd or belantamab mafodotin/Pd between Japanese and non-Japanese populations based on safety data from the DREAMM-7 and DREAMM-8 studies:

(1) DREAMM-7 study

Table 57 summarizes the safety data in non-Japanese patients and all Japanese patients (Japanese patients in the main cohort and patients in the Japan expansion cohort) from the DREAMM-7 study.

Table 57. Summary of differences in safety between Japanese and non-Japanese populations (DREAMM-7 study)

	Number of subjects (%)			
	Non-Japanese patients		All Japanese patients	
	Belantamab mafodotin/Bd N = 240	DAR/Bd N = 246	Belantamab mafodotin/Bd N = 12	DAR/Bd N = 14
All adverse events	240 (100)	246 (100)	12 (100)	14 (100)
Grade ≥3 adverse events	228 (95.0)	192 (78.0)	12 (100)	12 (85.7)
Adverse events leading to death	23 (9.6)	19 (7.7)	0	1 (7.1)
Serious adverse events	121 (50.4)	90 (36.6)	7 (58.3)	2 (14.3)
Adverse events leading to treatment discontinuation[*1] of the study drug	75 (31.3)	46 (18.7)	1 (8.3)	0
Adverse events leading to dose interruption[*2] of the study drug	226 (94.2)	185 (75.2)	11 (91.7)	12 (85.7)
Adverse events leading to dose reduction[*3] of the study drug	180 (75.0)	146 (59.3)	11 (91.7)	9 (64.3)

*1, Treatment discontinuation of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX; *2, dose interruption of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX; *3, dose reduction of one or more of the following: belantamab mafodotin, DAR, BOR, or DEX. (dose reduction criteria for DAR were not established)

Table 58 shows adverse events occurring in ≥2 patients at a higher incidence in Japanese patients than in non-Japanese patients in the belantamab mafodotin/Bd group in the DREAMM-7 study. No adverse events leading to death or treatment discontinuation were observed with an incidence ≥10% higher in Japanese patients compared to non-Japanese patients.

Table 58. Adverse events occurring in ≥2 patients at a higher incidence in Japanese patients than in non-Japanese patients in the belantamab mafodotin/Bd group (DREAMM-7 study)

PT (MedDRA ver.26.1)	Number of subjects (%)	
	All Japanese patients N = 12	Non-Japanese patients N = 240
Adverse events of any grade[*1]		
Injection site erythema	4 (33.3)	1 (0.4)
Decreased appetite	5 (41.7)	22 (9.2)
Malaise	4 (33.3)	2 (0.8)
Hepatic function abnormal	4 (33.3)	2 (0.8)
Vomiting	4 (33.3)	14 (5.8)
Diarrhoea	7 (58.3)	77 (32.1)
Sensation of foreign body	3 (25.0)	2 (0.8)
Foreign body sensation in eyes	8 (66.7)	105 (43.8)
Fall	3 (25.0)	5 (2.1)
Grade ≥3 adverse events[*2]		
Diarrhoea	3 (25.0)	9 (3.8)
Urinary tract infection	2 (16.7)	4 (1.7)
Thrombocytopenia	8 (66.7)	133 (55.4)
Lymphopenia	2 (16.7)	13 (5.4)
COVID-19	2 (16.7)	14 (5.8)
Serious adverse events[*2]		
COVID-19	2 (16.7)	11 (4.6)
Adverse events leading to dose interruption of any study drug[*2]		
Diarrhoea	3 (25.0)	20 (8.3)
Malaise	2 (16.7)	1 (0.4)
Dry eye	3 (25.0)	32 (13.3)
Pyrexia	2 (16.7)	16 (6.7)
Adverse events leading to dose reduction of any study drug[*2]		
Malaise	2 (16.7)	1 (0.4)
Diarrhoea	2 (16.7)	2 (0.8)
Thrombocytopenia	5 (41.7)	66 (27.5)

No adverse events leading to death or treatment discontinuation of any study drug were observed with an incidence ≥10% higher in Japanese patients compared to non-Japanese patients; *1, adverse events occurring at an incidence ≥20% higher; *2, adverse events occurring at an incidence ≥ 10% higher

(2) DREAMM-8 study

Table 59 summarizes the safety data in non-Japanese patients and all Japanese patients (Japanese patients in the main cohort and patients in the Japan expansion cohort) from the DREAMM-8 study.

Table 59. Summary of differences in safety between Japanese and non-Japanese populations (DREAMM-8 study)

	Number of subjects (%)			
	Non-Japanese patients		All Japanese patients	
	Belantamab mafodotin/Pd N = 147	VPd N = 139	Belantamab mafodotin/Pd N = 10	VPd N = 11
All adverse events	146 (99.3)	133 (95.7)	10 (100)	11 (100)
Grade ≥3 adverse events	138 (93.9)	104 (74.8)	10 (100)	9 (81.8)
Adverse events leading to death	17 (11.6)	15 (10.8)	1 (10.0)	1 (9.1)
Serious adverse events	93 (63.3)	61 (43.9)	5 (50.0)	4 (36.4)
Adverse events leading to treatment discontinuation[*1] of the study drug	22 (15.0)	15 (10.8)	1 (10.0)	4 (36.4)
Adverse events leading to dose interruption[*2] of the study drug	134 (91.2)	104 (74.8)	7 (70.0)	9 (81.8)
Adverse events leading to dose reduction[*3] of the study drug	90 (61.2)	84 (60.4)	6 (60.0)	5 (45.5)

*1, Treatment discontinuation of one or more of the following: belantamab mafodotin, POM, BOR, or DEX; *2, dose interruption of one or more of the following: belantamab mafodotin, POM, BOR, or DEX; *3, dose reduction of one or more of the following: belantamab mafodotin, POM, BOR, or DEX

Table 60 shows adverse events occurring in ≥2 patients at a higher incidence in Japanese patients than in non-Japanese patients in the belantamab mafodotin/Pd group in the DREAMM-8 study.

Table 60. Adverse events occurring in ≥2 patients at a higher incidence in Japanese patients than in non-Japanese patients in the belantamab mafodotin/Pd group (DREAMM-8 study)

PT (MedDRA ver.27.0)	Number of subjects (%)	
	All Japanese patients N = 10	Non-Japanese patients N = 147
Adverse events of any grade[*1]		
ALT increased	6 (60.0)	22 (15.0)
Constipation	5 (50.0)	21 (14.3)
AST increased	4 (40.0)	14 (9.5)
Malaise	3 (30.0)	1 (0.7)
ALP increased	3 (30.0)	7 (4.8)
Hypogammaglobulinaemia	3 (30.0)	8 (5.4)
Rash	3 (30.0)	10 (6.8)
Grade ≥3 adverse events[*2]		
Platelet count decreased	3 (30.0)	21 (14.3)
Anaemia	2 (20.0)	14 (9.5)
Adverse events leading to dose interruption of any study drug[*1]		
Rash	2 (20.0)	0

No adverse events leading to death, serious adverse events, adverse events leading to treatment discontinuation or dose reduction of any study drug that occurred at an incidence ≥20% higher in Japanese patients than in non-Japanese patients; *1, adverse events occurring at an incidence ≥20% higher; *2, adverse events occurring at an incidence ≥10% higher

In the DREAMM-7 and DREAMM-8 studies, adverse events of gastrointestinal disorders and hepatic dysfunction tended to occur more frequently in Japanese patients than in non-Japanese patients. For infections and cytopenias, the incidence of Grade ≥3 or serious adverse events was higher in Japanese patients than in non-Japanese patients. Although the limited number of Japanese patients in both studies makes it difficult to determine the reasons for the above differences, these adverse events were manageable by dose modification of belantamab mafodotin or other measures.

PMDA's view:

When belantamab mafodotin/Bd or belantamab mafodotin/Pd is administered, patients should be closely monitored for the serious adverse events and Grade ≥3 adverse events reported in the DREAMM-7 and DREAMM-8 studies. The applicant should provide information on the incidence of these adverse events to healthcare professionals using the package insert and other materials. Although the limited number of Japanese patients treated with belantamab mafodotin/Bd or belantamab mafodotin/Pd makes it difficult to fully evaluate potential differences in the safety of belantamab mafodotin between Japanese and non-Japanese populations, vigilance is required for adverse events that occurred at a higher incidence in Japanese patients than in non-Japanese patients. The applicant should provide information on the incidence of these adverse events to healthcare professionals using the package insert and other materials.

In the following sections, PMDA reviewed safety focusing on frequently reported adverse events, serious adverse events, and adverse events that led to death in the DREAMM-7 and DREAMM-8 studies based on data from these studies, as well as cautionary statements on adverse events included in the

package inserts of belantamab mafodotin in other countries.[77)] Results from the DREAMM-3 study, which evaluated belantamab mafodotin monotherapy, were also taken into consideration.

7.R.3.2 Eye disorders

The applicant's explanation about the incidence of eye disorders and eye disorder-related safety measures:

(1) Incidence of eye disorders

Table 61 and Table 62 show the incidence of eye disorders[78)] in the DREAMM-7 and DREAMM-8 studies.

Table 61. Incidence of eye disorders occurring in ≥10% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders[*2]	196 (81.0)	92 (38.0)	100 (40.7)	14 (5.7)	136 (90.7)	73 (48.7)	55 (37.9)	9 (6.2)
Vision blurred	160 (66.1)	53 (21.9)	26 (10.6)	2 (0.8)	119 (79.3)	26 (17.3)	22 (15.2)	0
Dry eye	123 (50.8)	17 (7.0)	17 (6.9)	0	91 (60.7)	12 (8.0)	14 (9.7)	0
Photophobia	114 (47.1)	5 (2.1)	6 (2.4)	0	66 (44.0)	5 (3.3)	6 (4.1)	0
Eye irritation	103 (42.6)	12 (5.0)	13 (5.3)	0	75 (50.0)	6 (4.0)	13 (9.0)	0
Foreign body sensation in eyes	106 (43.8)	8 (3.3)	10 (4.1)	0	91 (60.7)	9 (6.0)	9 (6.2)	0
Eye pain	77 (31.8)	2 (0.8)	8 (3.3)	1 (0.4)	49 (32.7)	3 (2.0)	7 (4.8)	0
Cataract	49 (20.2)	17 (7.0)	25 (10.2)	6 (2.4)	40 (26.7)	9 (6.0)	15 (10.3)	6 (4.1)
Visual impairment	26 (10.7)	13 (5.4)	4 (1.6)	1 (0.4)	23 (15.3)	15 (10.0)	2 (1.4)	1 (0.7)
Visual acuity reduced	14 (5.8)	4 (1.7)	5 (2.0)	1 (0.4)	34 (22.7)	20 (13.3)	8 (5.5)	1 (0.7)
Punctate keratitis	2 (0.8)	1 (0.4)	1 (0.4)	0	34 (22.7)	9 (6.0)	1 (0.7)	1 (0.7)
Corneal epithelial microcysts	1 (0.4)	1 (0.4)	0	0	34 (22.7)	12 (8.0)	0	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 62. Incidence of serious eye disorders, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Eye disorders leading to death	0	0	0	0
Serious eye disorders	2 (0.8)	1 (0.4)	1 (0.7)	1 (0.7)
Cataract	1 (0.4)	0	0	1 (0.7)
Malignant neoplasm of conjunctiva	1 (0.4)	0	0	0
Vision blurred	0	1 (0.4)	0	0
Diplopia	0	0	1 (0.7)	0
Serious eye disorders for which a causal relationship to the study drug could not be ruled out	1 (0.4)	0	0	0
Cataract	1 (0.4)	0	0	0

77) The package inserts of belantamab mafodotin (monotherapy) in the US and Europe included cautionary statements regarding eye disorders, thrombocytopenia, pneumonia, and infusion reaction. However, the authorization was subsequently withdrawn [see Section 1.2].

78) In addition to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) "eye disorders," 172 MedDRA preferred terms (PTs) were added as adverse events of special interest (see CTD2.7.4 Appendix 3).

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Eye disorders leading to treatment discontinuation of any study drug[*2]	8 (3.3)	1 (0.4)	6 (4.0)	0
Vision blurred	5 (2.1)	0	1 (0.7)	0
Keratopathy	1 (0.4)	0	2 (1.3)	0
Eye disorders leading to dose interruption of any study drug[*3]	126 (52.1)	3 (1.2)	96 (64.0)	7 (4.8)
Vision blurred	80 (33.1)	1 (0.4)	55 (36.7)	0
Dry eye	33 (13.6)	0	32 (21.3)	0
Photophobia	33 (13.6)	0	22 (14.7)	0
Eye irritation	32 (13.2)	0	24 (16.0)	1 (0.7)
Foreign body sensation in eyes	30 (12.4)	0	25 (16.7)	0
Eye pain	25 (10.3)	1 (0.4)	19 (12.7)	0
Visual acuity reduced	7 (2.9)	0	26 (17.3)	0
Visual impairment	17 (7.0)	0	15 (10.0)	0
Eye disorders leading to dose reduction of any study drug[*4]	53 (21.9)	2 (0.8)	9 (6.0)	0
Vision blurred	27 (11.2)	2 (0.8)	3 (2.0)	0
Visual impairment	7 (2.9)	0	1 (0.7)	0
Dry eye	6 (2.5)	0	0	0
Eye pain	5 (2.1)	0	0	0
Photophobia	5 (2.1)	0	0	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group; *3, adverse events occurring in ≥10% of subjects in either belantamab mafodotin group; *4, adverse events occurring in ≥2% of subjects in either belantamab mafodotin group

In the Japan expansion cohort in the DREAMM-7 study, no eye disorders led to death in the belantamab mafodotin/Bd group. Serious eye disorders occurred in 2 subjects in the belantamab mafodotin/Bd group (20%; cataract and eyelid infection in 1 subject each), and a causal relationship to the study drug was ruled out for both events. The incidence of eye disorders leading to treatment discontinuation, dose interruption, or dose reduction of any study drug in the belantamab mafodotin/Bd group was 0%, 30% (3 of 10 subjects), and 0%, respectively.

In the Japan expansion cohort in the DREAMM-8 study, no eye disorders led to death in the belantamab mafodotin/Pd group. Serious eye disorders occurred in 1 subject in the belantamab mafodotin/Pd group (cytomegalovirus chorioretinitis), and a causal relationship to the study drug was ruled out. The incidence of eye disorders leading to treatment discontinuation, dose interruption, or dose reduction of any study drug in the belantamab mafodotin/Pd group was 0%, 42.9% (3 of 7 subjects), or 14.3% (1 of 7 subjects), respectively.

In the DREAMM-3 study, no eye disorders led to death and there were no serious eye disorders. The incidence of eye disorders leading to treatment discontinuation, dose interruption, or dose reduction of any study drug in the belantamab mafodotin group was 2.8% (6 of 217 subjects), 34.1% (74 of 217 subjects), and 28.1% (61 of 217 subjects), respectively.

Among subjects who developed adverse events classified as ulcerative keratitis, blindness, and corneal perforation,[79] no subjects had outcomes reported as "not resolved" or "with sequelae" in any of the DREAMM-7, DREAMM-8, or DREAMM-3 study.

In the belantamab mafodotin group, the median time to initial onset (number of days from the first dose) of eye disorder events (Min, Max) in the DREAMM-7, DREAMM-8, and DREAMM-3 studies was 41.0 (1, 752), 29.0 (1, 273), and 40.0 (1, 607), respectively.

The effects of belantamab mafodotin on vision and its reversibility are discussed below.
In the DREAMM-7 and DREAMM-8 studies, ophthalmologic examinations[80] were performed using KVA scale [for specific assessment/judgment methods, see the dose modification criteria in the "Corneal examination findings and vision changes" in Section "7.R.5.2 Dose modification of belantamab mafodotin"]. Based on the results of ophthalmologic examinations, the dose of belantamab mafodotin was to be adjusted.

Table 63 shows the effects of belantamab mafodotin treatment on vision in patients with normal baseline vision (unilateral vision of at least 20/25), as measured by the proportion of patients experiencing bilateral worsening of Snellen scores to 20/50 (0.4 decimal visual acuity) or 20/200 (0.1 decimal visual acuity) or lower, and the status of recovery. The proportion of patients who underwent dose reduction of belantamab mafodotin based on the ophthalmologic examination results was 44% (106 of 242 subjects) (reduced to 1.9 mg/kg Q3W) in the DREAMM-7 study, and 59% (88 of 150 subjects) (reduced to 1.9 or 1.4 mg/kg Q8W) in the DREAMM-8 study. The proportion of patients who underwent dose interruption of belantamab mafodotin was 78% (189 of 242 subjects) in the DREAMM-7 study and 83% (124 of 150 subjects) in the DREAMM-8 study. The proportion of patients whose treatment with belantamab mafodotin was discontinued was 9% in both DREAMM-7 and DREAMM-8 studies (22 of 242 subjects and 14 of 150 subjects, respectively).

[79] MedDRA PT
[80] The KVA scale is an assessment scale system developed through discussion with ophthalmologists. The scale can be used to evaluate corneal findings in addition to vision change. In both DREAMM-7 and DREAMM-8 studies, the Common Terminology Criteria for Adverse Events (CTCAE) scale (scale system to grade corneal disorder per CTCAE v 5.0 and vision change) was used for dose modification at the start of the study. In Protocol Amendment 1 (dated July 16, 2020 for the DREAMM-7 study and April 20, 2021 for the DREAMM-8 study), the assessment method was changed to the KVA scale.

Table 63. Summary of visual acuity reduced associated with belantamab mafodotin and the recovery status (DREAMM-7 and DREAMM-8 studies)

	≤20/50 (0.4 decimal visual acuity)		≤20/200 (0.1 decimal visual acuity)	
	DREAMM-7	DREAMM-8	DREAMM-7	DREAMM-8
	Belantamab mafodotin/Bd N = 242	Belantamab mafodotin/Pd N = 150	Belantamab mafodotin/Bd N = 242	Belantamab mafodotin/Pd N = 150
Number of subjects experiencing worsening to ≤20/50 or 20/200 (%)	82 (33.9)	51 (34.0)	5 (2.1)	2 (1.3)
Outcome, n (%)				
Resolved before the completion of belantamab mafodotin treatment	71 (86.6)	38 (74.5)	3 (60.0)	1 (50.0)
Resolved after the completion of belantamab mafodotin treatment	6 (7.3)	5 (9.8)	1 (20.0)	0
Not resolved as of the final follow-up period[*1] (study data cut-off date)	5 (6.1)	8 (15.7)	1 (20.0)	1 (50.0)
Median time to initial onset (days) (median [Min, Max])	73.5 [16, 753]	112 [28, 761]	105 [47, 304]	351 [29, 673]
Duration of events[*2] (days) (median [Min, Max])	64.0 [8, 908]	57.0 [14, 451]	86.5 [22, 194]	57.0[*3]

*1, final follow-up of individual patients up to data cut-off date in each study; *2, time from onset of visual acuity reduced (≤20/50 or 20/200) to the time vision resolved to unilateral ≥20/25; *3, individual values

Of the subjects who had not recovered by the end of the follow-up period shown in Table 63, 1 of the 5 subjects in the DREAMM-7 study had discontinued treatment and was still undergoing follow-up as of the data cut-off date (subsequently died; unknown course of visual acuity), and the other 4 subjects had discontinued treatment of belantamab mafodotin and completed the follow-up period as of the data cut-off date (course of visual acuity after the follow-up period is unknown). Of the 8 subjects in the DREAMM-8 study, 2 subjects resumed belantamab mafodotin after the data cut-off date and the ophthalmologic examination showed vision recovery (20/20), 1 subject did not resume treatment after the data cut-off date and vision did not recover (20/40), 1 subject discontinued treatment and was still undergoing follow-up as of the data cut-off date (vision data are not available), and the remaining 4 subjects discontinued treatment of belantamab mafodotin and completed follow-up as of the data cut-off date (course of visual acuity after the follow-up period is unknown).

(2) Eye disorder-related safety measures

(i) Prevention of eye disorders

In the DREAMM-7 and DREAMM-8 studies, the following measures were taken:

- Administration of preservative-free artificial tears (≥4 times daily) (required for all subjects)
- Administration of corticosteroid eye drops (optional)
- Use of cooling eye masks (optional)
- Avoid using contact lenses

In all clinical studies of belantamab mafodotin including the DREAMM-7 and DREAMM-8 studies, artificial tears must be administered to mitigate dry eye and other eye symptoms caused by belantamab mafodotin. However, there was no clear benefit from the use of corticosteroid eye drops in the

DREAMM-2 ocular sub-study[81]; therefore, its use was optional in the DREAMM-7 and DREAMM-8 studies, in which the use of cooling eye masks was also optional.

(ii) Examination of eye disorders and actions

The following steps were taken in the DREAMM-7 and DREAMM-8 studies:

- Patients with corneal epithelial disease except for mild punctate keratopathy were listed in the exclusion criteria
- Ophthalmologic examination and monitoring in coordination with an ophthalmologist [see Section 7.R.5.2].
- Evaluation of eye disorders using the KVA scale and dose modification of belantamab mafodotin (treatment discontinuation, dose interruption, dose reduction) [see Section 7.R.5.2]

Based on the measures to prevent eye disorders, ophthalmologic examination, and actions implemented in the DREAMM-7 and DREAMM-8 studies, belantamab mafodotin was demonstrated to have a tolerable safety profile. Therefore, the package insert will include recommendations for regular ophthalmologic examinations in collaboration with an ophthalmologist, dose modifications of belantamab mafodotin based on the examination results, and use of artificial tears to mitigate eye symptoms.

In addition, given the high frequency of eye disorders that may lead to worsening of visual acuity, such as vision blurred, associated with belantamab mafodotin (Table 61),[82] a cautionary statement to the effect that patients should be instructed to take precautions when operating heavy machinery or driving vehicles will be included in the package insert.

PMDA's view:

Eye disorders occurred frequently and adverse events causing reduced visual acuity were reported in association with belantamab mafodotin treatment in the clinical studies. Given these circumstances, when belantamab mafodotin is used, patients should be monitored closely for the development of eye disorders. PMDA concluded that information on the incidence of eye disorders in the clinical studies and cautionary statements should be provided to healthcare professionals by using the package insert to ensure that when belantamab mafodotin is used, ophthalmologic examinations should be performed in collaboration with an ophthalmologist and if any abnormalities are detected, treatment discontinuation or other measures are taken by healthcare professionals.

7.R.3.3 Cytopenia

The applicant's explanation about cytopenia associated with belantamab mafodotin treatment:

To evaluate cytopenia-related adverse events, events classified as MedDRA Standardized Medical

[81] In the first 4 cycles, patients were to administer corticosteroid eye drops in one eye only. The incidence of corneal-related adverse events was 70.6% (12 of 17 subjects) with or without eye drops (belantamab mafodotin 2.5 mg/kg).

[82] According to the questionnaires (qualitative evaluation) administered to patients in the clinical studies, 40% and 34% of patients in the DREAMM-7 study and DREAMM-8 study (belantamab mafodotin group), respectively, stopped driving due to eyesight issues during the study period.

Dictionary for Regulatory Activities query (SMQ) “haematopoietic cytopenias (broad)” were collected.

Table 64 and Table 65 show the incidence of cytopenia in the DREAMM-7 and DREAMM-8 studies.

Table 64. Incidence of cytopenia occurring in ≥5% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT*1	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cytopenia*2	218 (90.1)	188 (77.7)	185 (75.2)	133 (54.1)	119 (79.3)	102 (68.0)	92 (63.4)	73 (50.3)
Thrombocytopenia	167 (69.0)	134 (55.4)	122 (49.6)	87 (35.4)	54 (36.0)	36 (24.0)	44 (30.3)	29 (20.0)
Anaemia	46 (19.0)	20 (8.3)	65 (26.4)	25 (10.2)	35 (23.3)	15 (10.0)	38 (26.2)	19 (13.1)
Platelet count decreased	51 (21.1)	44 (18.2)	40 (16.3)	26 (10.6)	30 (20.0)	22 (14.7)	22 (15.2)	18 (12.4)
Neutropenia	34 (14.0)	30 (12.4)	27 (11.0)	15 (6.1)	72 (48.0)	63 (42.0)	50 (34.5)	41 (28.3)
Lymphopenia	21 (8.7)	13 (5.4)	23 (9.3)	17 (6.9)	7 (4.7)	4 (2.7)	3 (2.1)	2 (1.4)
Leukopenia	14 (5.8)	6 (2.5)	10 (4.1)	6 (2.4)	7 (4.7)	3 (2.0)	5 (3.4)	1 (0.7)
Neutrophil count decreased	9 (3.7)	4 (1.7)	14 (5.7)	6 (2.4)	31 (20.7)	31 (20.7)	19 (13.1)	18 (12.4)

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 65. Incidence of serious cytopenia, etc. (DREAMM-7 and DREAMM-8 studies)

PT*1	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Cytopenia leading to death	1 (0.4)	0	0	0
Febrile neutropenia	1 (0.4)	0	0	0
Cytopenia leading to death for which a causal relationship to the study drug could not be ruled out	0	0	0	0
Serious cytopenia	15 (6.2)	8 (3.3)	19 (12.7)	11 (7.6)
Thrombocytopenia	8 (3.3)	4 (1.6)	1 (0.7)	5 (3.4)
Anaemia	4 (1.7)	3 (1.2)	1 (0.7)	1 (0.7)
Platelet count decreased	3 (1.2)	0	1 (0.7)	1 (0.7)
Febrile neutropenia	1 (0.4)	1 (0.4)	5 (3.3)	3 (2.1)
Neutropenia	0	0	9 (6.0)	4 (2.8)
Neutropenic sepsis	0	0	2 (1.3)	2 (1.4)
White blood cell count decreased	0	0	2 (1.3)	0
Neutrophil count decreased	0	0	1 (0.7)	0
Pancytopenia	0	0	1 (0.7)	0
Serious cytopenia for which a causal relationship to the study drug could not be ruled out	11 (4.5)	5 (2.0)	16 (10.7)	9 (6.2)
Thrombocytopenia	8 (3.3)	4 (1.6)	1 (0.7)	3 (2.1)
Anaemia	1 (0.4)	1 (0.4)	1 (0.7)	0
Platelet count decreased	3 (1.2)	0	1 (0.7)	1 (0.7)
Febrile neutropenia	0	0	4 (2.7)	3 (2.1)
Neutropenia	0	0	8 (5.3)	4 (2.8)
Neutropenic sepsis	0	0	2 (1.3)	2 (1.4)
White blood cell count decreased	0	0	1 (0.7)	0
Pancytopenia	0	0	1 (0.7)	0
Cytopenia leading to treatment discontinuation of any study drug*2	10 (4.1)	2 (0.8)	0	0
Thrombocytopenia	5 (2.1)	2 (0.8)	0	0
Cytopenia leading to dose interruption of any study drug*2	120 (49.6)	72 (29.3)	61 (40.7)	37 (25.5)
Thrombocytopenia	85 (35.1)	50 (20.3)	8 (5.3)	12 (8.3)
Platelet count decreased	28 (11.6)	13 (5.3)	10 (6.7)	7 (4.8)
Neutropenia	15 (6.2)	6 (2.4)	35 (23.3)	13 (9.0)
Anaemia	3 (1.2)	6 (2.4)	7 (4.7)	5 (3.4)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Neutrophil count decreased	3 (1.2)	0	15 (10.0)	8 (5.5)
Febrile neutropenia	0	0	3 (2.0)	2 (1.4)
Cytopenia leading to dose reduction of any study drug*2	92 (38.0)	33 (13.4)	47 (31.3)	20 (13.8)
Thrombocytopenia	67 (27.7)	24 (9.8)	6 (4.0)	9 (6.2)
Platelet count decreased	22 (9.1)	8 (3.3)	6 (4.0)	1 (0.7)
Neutropenia	3 (1.2)	1 (0.4)	21 (14.0)	6 (4.1)
Neutrophil count decreased	1 (0.4)	0	15 (10.0)	5 (3.4)

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in ≥2% of subjects in either belantamab mafodotin group

In the Japan expansion cohort in the DREAMM-7 study, there were no cytopenia events leading to death and no serious cases of cytopenia in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no cases of cytopenia leading to death and no serious cases of cytopenia in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, there were no cases of cytopenia that led to death. Serious cytopenia occurred in 21 subjects in the belantamab mafodotin group (9.7% total; thrombocytopenia [9 subjects], anaemia [6 subjects], platelet count decreased [4 subjects], febrile neutropenia [1 subject], neutropenia [1 subject], and neutrophil count decreased [1 subject]; some patients were counted more than once). Among these, a causal relationship to belantamab mafodotin could not be ruled out for 14 subjects (6.5% total; thrombocytopenia [6 subjects], platelet count decreased [4 subjects], anaemia [2 subjects], neutropenia [1 subject], and neutrophil count decreased [1 subject]).

PMDA's view:

Thrombocytopenia occurred frequently in the DREAMM-7 and DREAMM-8 studies; serious thrombocytopenia for which a causal relationship to the study drug could not be ruled out occurred in multiple subjects; in the DREAMM-8 study, serious neutropenia and febrile neutropenia for which a causal relationship to the study drug could not be ruled out occurred in multiple subjects; and in the DREAMM-3 study in which belantamab mafodotin monotherapy was evaluated, serious anaemia for which a causal relationship to belantamab mafodotin could not be ruled out occurred in multiple subjects. Based on the above and other factors, patients should be closely monitored for cytopenia when belantamab mafodotin is administered. Therefore, it was concluded that information on the incidence of cytopenia in the clinical studies should be provided in an appropriate manner to healthcare professionals and that appropriate cautionary statements should be included in the package insert to the effect that regular hematological examinations should be performed during treatment with belantamab mafodotin to ensure that appropriate measures are taken if any abnormalities are detected.

7.R.3.4 Infections

The applicant's explanation about the infections associated with belantamab mafodotin treatment:

To evaluate infection-related adverse events, events classified as MedDRA SOC "Infections and infestations" were collected.

Table 66 and Table 67 show the incidence of infections in the DREAMM-7 and DREAMM-8 studies.

Table 66. Infections occurring in ≥5% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections[*2]	170 (70.2)	75 (31.0)	166 (67.5)	49 (19.9)	123 (82.0)	73 (48.7)	99 (68.3)	38 (26.2)
COVID-19	58 (24.0)	14 (5.8)	49 (19.9)	11 (4.5)	56 (37.3)	10 (6.7)	31 (21.4)	3 (2.1)
Upper respiratory tract infection	48 (19.8)	0	49 (19.9)	0	40 (26.7)	2 (1.3)	25 (17.2)	0
Pneumonia	44 (18.2)	28 (11.6)	22 (8.9)	10 (4.1)	36 (24.0)	26 (17.3)	17 (11.7)	11 (7.6)
Urinary tract infection	21 (8.7)	4 (1.7)	20 (8.1)	1 (0.4)	23 (15.3)	6 (4.0)	13 (9.0)	1 (0.7)
Bronchitis	23 (9.5)	2 (0.8)	15 (6.1)	2 (0.8)	12 (8.0)	3 (2.0)	7 (4.8)	1 (0.7)
COVID-19 pneumonia	8 (3.3)	8 (3.3)	11 (4.5)	9 (3.7)	18 (12.0)	16 (10.7)	6 (4.1)	6 (4.1)
Nasopharyngitis	11 (4.5)	0	6 (2.4)	0	9 (6.0)	0	7 (4.8)	0
Respiratory tract infection	10 (4.1)	1 (0.4)	8 (3.3)	1 (0.4)	8 (5.3)	3 (2.0)	7 (4.8)	0
Influenza	8 (3.3)	0	11 (4.5)	1 (0.4)	8 (5.3)	0	6 (4.1)	2 (1.4)
Viral infection	1 (0.4)	0	0	0	8 (5.3)	2 (1.3)	3 (2.1)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 67. Incidence of serious infections, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Infections leading to death[*2]	19 (7.9)	15 (6.1)	11 (7.3)	9 (6.2)
Pneumonia	7 (2.9)	2 (0.8)	2 (1.3)	1 (0.7)
COVID-19	3 (1.2)	5 (2.0)	2 (1.3)	2 (1.4)
COVID-19 pneumonia	2 (0.8)	5 (2.0)	5 (3.3)	2 (1.4)
Sepsis	3 (1.2)	3 (1.2)	0	2 (1.4)
Infections leading to death for which a causal relationship to the study drug could not be ruled out[*3]	4 (1.7)	2 (0.8)	2 (1.3)	0
Pneumonia	4 (1.7)	0	1 (0.7)	0
COVID-19	0	2 (0.8)	0	0
Serious infections[*4]	71 (29.3)	47 (19.1)	74 (49.3)	37 (25.5)
Pneumonia	27 (11.2)	10 (4.1)	27 (18.0)	11 (7.6)
COVID-19	11 (4.5)	10 (4.1)	10 (6.7)	4 (2.8)
COVID-19 pneumonia	8 (3.3)	8 (3.3)	17 (11.3)	6 (4.1)
Urinary tract infection	2 (0.8)	0	5 (3.3)	0
Pneumocystis jirovecii pneumonia	0	0	3 (2.0)	0
Respiratory tract infection	1 (0.4)	1 (0.4)	3 (2.0)	0
Serious infections for which a causal relationship to the study drug could not be ruled out[*5]	15 (6.2)	14 (5.7)	30 (20.0)	11 (7.6)
Pneumonia	9 (3.7)	4 (1.6)	17 (11.3)	4 (2.8)
COVID-19	1 (0.4)	3 (1.2)	0	0
COVID-19 pneumonia	1 (0.4)	0	0	1 (0.7)
Pneumocystis jirovecii pneumonia	0	0	3 (2.0)	0
Infections leading to dose interruption of any study drug[*6]	113 (46.7)	96 (39.0)	104 (69.3)	64 (44.1)
COVID-19	37 (15.3)	27 (11.0)	42 (28.0)	22 (15.2)
Upper respiratory tract infection	27 (11.2)	25 (10.2)	20 (13.3)	20 (13.8)
Pneumonia	24 (9.9)	12 (4.9)	25 (16.7)	12 (8.3)
Bronchitis	16 (6.6)	6 (2.4)	8 (5.3)	2 (1.4)
COVID-19 pneumonia	7 (2.9)	5 (2.0)	14 (9.3)	3 (2.1)

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group; *3, among events listed in the table as infections leading to death, those for which a causal relationship to the study drug could not be ruled out; *4, adverse events occurring in ≥2% of subjects in either belantamab mafodotin group; *5, among events listed in the table as serious infections, those for which a causal relationship to the study drug could not be ruled out; *6, adverse events occurring in ≥5% of subjects in either belantamab mafodotin group. No infections led to treatment discontinuation or dose reduction of any study drug.

In the Japan expansion cohort in the DREAMM-7 study, there were no infections that led to death in the belantamab mafodotin/Bd group. Serious infections occurred in 4 subjects in the belantamab mafodotin/Bd group (40% total; COVID-19 [2 subjects]; eyelid infection, pneumonia, pneumonia pneumococcal, sepsis, urinary tract infection [1 subject each]). Among these events, a causal relationship to the study drug could not be ruled out for pneumonia and pneumonia pneumococcal (1 subject each).

In the Japan expansion cohort in the DREAMM-8 study, infection led to death in 1 subject in the belantamab mafodotin/Pd group (14.3%, morganella infection), for which a causal relationship to the study drug was ruled out. Serious infections occurred in 3 subjects in the belantamab mafodotin/Pd group (42.9% total; cytomegalovirus chorioretinitis, morganella infection, and pneumocystis jirovecii pneumonia [1 subject each]). Among these events, a causal relationship to the study drug could not be ruled out for pneumocystis jirovecii pneumonia.

In the DREAMM-3 study, infections led to death in 7 subjects in the belantamab mafodotin group (3.2% total; sepsis and septic shock [2 subjects each]; COVID-19, pneumonia, and respiratory tract infection [1 subject each]), and a causal relationship to belantamab mafodotin was ruled out for all events. Serious infections occurred in 30 subjects in the belantamab mafodotin group (13.8% total; pneumonia [7 subjects]; COVID-19 [5 subjects]; COVID-19 pneumonia, septic shock, and urinary tract infection [3 subjects each]; sepsis, lower respiratory tract infection and osteomyelitis [2 subjects each]; respiratory tract infection, rhinovirus infection, cellulitis, pneumonia influenzal, pneumonia pneumococcal, postoperative wound infection, pseudomembranous colitis, spontaneous bacterial peritonitis, and upper respiratory tract infection [1 subject each]; some patients were counted more than once). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for pneumonia, urinary tract infection, pneumonia influenzal, and upper respiratory tract infection [1 subject each]).

PMDA's view:
In the DREAMM-3, DREAMM-7, and DREAMM-8 studies, pneumonia, urinary tract infection, and other infections leading to death and serious infections for which a causal relationship to belantamab mafodotin could not be ruled out occurred in multiple subjects. Based on the above and other factors, patients should be closely monitored for infections when belantamab mafodotin is administered. Therefore, it was concluded that information on the incidence of infections in the clinical studies should be provided in an appropriate manner to healthcare professionals using the package insert and other materials.

7.R.3.5 Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with belantamab mafodotin:
To evaluate gastrointestinal disorder-related adverse events, events classified as MedDRA SOC "gastrointestinal disorders" were collected.

Table 68 and Table 69 show the incidence of gastrointestinal disorders in the DREAMM-7 and DREAMM-8 studies.

Table 68. Gastrointestinal disorders occurring in ≥5% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastrointestinal disorders[*2]	154 (63.6)	32 (13.2)	153 (62.2)	23 (9.3)	75 (50.0)	16 (10.7)	82 (56.6)	17 (11.7)
Diarrhoea	78 (32.2)	9 (3.7)	77 (31.3)	10 (4.1)	35 (23.3)	2 (1.3)	33 (22.8)	10 (6.9)
Constipation	46 (19.0)	2 (0.8)	56 (22.8)	1 (0.4)	23 (15.3)	2 (1.3)	33 (22.8)	2 (1.4)
Nausea	39 (16.1)	2 (0.8)	30 (12.2)	0	18 (12.0)	1 (0.7)	16 (11.0)	0
Vomiting	15 (6.2)	2 (0.8)	24 (9.8)	0	7 (4.7)	0	7 (4.8)	0
Abdominal pain	20 (8.3)	3 (1.2)	13 (5.3)	1 (0.4)	5 (3.3)	0	4 (2.8)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 69. Incidence of serious gastrointestinal disorders, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Gastrointestinal disorders leading to death[*2]	3 (1.2)	0	1 (0.7)	1 (0.7)
Colitis	1 (0.4)	0	0	0
Gastrointestinal haemorrhage	1 (0.4)	0	0	0
Peritonitis	1 (0.4)	0	0	0
Thrombosis mesenteric vessel	1 (0.4)	0	0	0
Gastrointestinal cancer metastatic	0	0	1 (0.7)	0
Gastrointestinal disorders leading to death for which a causal relationship to the study drug could not be ruled out	2 (0.8)	0	1 (0.7)	0
Gastrointestinal haemorrhage	1 (0.4)	0	0	0
Thrombosis mesenteric vessel	1 (0.4)	0	0	0
Gastrointestinal cancer metastatic	0	0	1 (0.7)	0
Serious gastrointestinal disorders[*3]	23 (9.5)	13 (5.3)	14 (9.3)	7 (4.8)
Diarrhoea	3 (1.2)	0	1 (0.7)	1 (0.7)
Pancreatitis acute	0	0	2 (1.3)	0
Ascites	0	0	2 (1.3)	0
Serious gastrointestinal disorders for which a causal relationship to the study drug could not be ruled out[*4]	6 (2.5)	6 (2.4)	5 (3.3)	3 (2.1)
Diarrhoea	1 (0.4)	0	0	1 (0.7)
Ascites	0	0	1 (0.7)	0
Gastrointestinal disorders leading to treatment discontinuation of any study drug[*5]	4 (1.7)	4 (1.6)	1 (0.7)	2 (1.4)
Gastrointestinal disorders leading to dose interruption of any study drug[*5]	40 (16.5)	46 (18.7)	26 (17.3)	24 (16.6)
Diarrhoea	20 (8.3)	21 (8.5)	6 (4.0)	12 (8.3)
Vomiting	4 (1.7)	4 (1.6)	4 (2.7)	1 (0.7)
Pharyngitis	1 (0.4)	3 (1.2)	3 (2.0)	1 (0.7)
Gastrointestinal disorders leading to dose reduction of any study drug[*5]	13 (5.4)	16 (6.5)	6 (4.0)	11 (7.6)
Dyspepsia	3 (1.2)	2 (0.8)	3 (2.0)	1 (0.7)

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in either belantamab mafodotin group; *3, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group; *4, among events listed in the table as serious gastrointestinal disorders, those for which a causal relationship to the study drug could not be ruled out; *5, adverse events occurring in ≥2% of subjects in either belantamab mafodotin group. No gastrointestinal disorders led to treatment discontinuation of any study drug.

In the Japan expansion cohort in the DREAMM-7 study, no gastrointestinal disorders led to death in the belantamab mafodotin/Bd group. A serious gastrointestinal disorder occurred in 1 subject in the belantamab mafodotin/Bd group (10%, large intestine polyp), for which a causal relationship to the study drug was ruled out.

In the Japan expansion cohort in the DREAMM-8 study, there were no gastrointestinal disorders leading to death and no serious gastrointestinal disorders in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, a gastrointestinal disorder led to death in 1 subject in the belantamab mafodotin group (0.5%, abdominal compartment syndrome), for which a causal relationship to belantamab mafodotin was ruled out. Serious gastrointestinal disorders occurred in 9 subjects in the belantamab mafodotin group (4.1% total; gastrointestinal haemorrhage and vomiting [2 subjects each]; abdominal compartment syndrome, colitis, gastric haemorrhage, haematochezia, pseudomembranous colitis, small intestinal haemorrhage, and spontaneous bacterial peritonitis [1 subject each]; some

patients were counted more than once). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for vomiting (1 subject).

Table 70 shows details of patients who developed serious gastrointestinal disorders for which a causal relationship to belantamab mafodotin could not be ruled out in the DREAMM-3, DREAMM-7, and DREAMM-8 studies.

Table 70. List of patients who developed serious gastrointestinal disorders for which a causal relationship to belantamab mafodotin could not be ruled out

Study	Age	Sex	PT	Grade	Onset day	Duration (days)	Treatment change*	Outcome
DREAMM-3	6[redacted]	F	Vomiting	2	82	5	Not applicable	Resolved
DREAMM-7	6[redacted]	M	Constipation	2	36	3	No change	Resolved
	5[redacted]	F	Thrombosis mesenteric vessel	5	8	2	Treatment discontinuation, dose interruption/delay	Death
	7[redacted]	F	Vomiting	2	48	1	Dose interruption/delay	Resolved
DREAMM-8	6[redacted]	M	Oral candidiasis	1	270	2	No change	Resolved
	5[redacted]	F	Gastroenteritis	3	844	-	No change	Resolving

*, Treatment of belantamab mafodotin (DREAMM-3 and DREAMM-8 studies) or any study drug (DREAMM-7 study)

PMDA's view:

The limited number of subjects with serious gastrointestinal disorders after administration of belantamab mafodotin in the DREAMM-3, DREAMM-7, and DREAMM-8 studies makes it difficult to determine conclusively as to whether belantamab mafodotin/Bd or belantamab mafodotin/Pd is associated with gastrointestinal disorders. However, given that there were serious gastrointestinal disorders for which a causal relationship to belantamab mafodotin could not be ruled out, it was concluded that information on the incidence of gastrointestinal disorders in the clinical studies should be included in the package insert and other materials. In addition, the applicant should continue to collect post-marketing data on these events, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.6 Bleeding

The applicant's explanation about bleeding associated with belantamab mafodotin:

To evaluate bleeding-related adverse events, events classified as MedDRA SMQ "haemorrhage terms (excl laboratory terms) (narrow)" were collected.

Table 71 and Table 72 show the incidence of bleeding in the DREAMM-7 and DREAMM-8 studies.

Table 71. Bleeding occurring in ≥2% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Bleeding[*2]	43 (17.8)	9 (3.7)	29 (11.8)	6 (2.4)	29 (19.3)	2 (1.3)	22 (15.2)	2 (1.4)
Epistaxis	9 (3.7)	0	7 (2.8)	2 (0.8)	11 (7.3)	0	5 (3.4)	0
Contusion	7 (2.9)	0	7 (2.8)	0	2 (1.3)	0	6 (4.1)	0
Haematoma	7 (2.9)	0	1 (0.4)	0	1 (0.7)	0	1 (0.7)	0
Retinal haemorrhage	2 (0.8)	0	1 (0.4)	0	3 (2.0)	0	0	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 72. Incidence of serious bleeding, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Bleeding leading to death[*2]	3 (1.2)	1 (0.4)	0	0
Cerebral haemorrhage	1 (0.4)	0	0	0
Gastrointestinal haemorrhage	1 (0.4)	0	0	0
Subdural haemorrhage	1 (0.4)	0	0	0
Bleeding leading to death for which a causal relationship to the study drug could not be ruled out	2 (0.8)	0	0	0
Gastrointestinal haemorrhage	1 (0.4)	0	0	0
Subdural haemorrhage	1 (0.4)	0	0	0
Serious bleeding[*2]	9 (3.7)	2 (0.8)	2 (1.3)	2 (1.4)
Gastrointestinal haemorrhage	1 (0.4)	1 (0.4)	1 (0.7)	1 (0.7)
Cerebral haemorrhage	1 (0.4)	0	0	1 (0.7)
Gastrointestinal polyp haemorrhage	1 (0.4)	0	0	0
Haematoma	1 (0.4)	0	0	0
Haematuria	1 (0.4)	0	0	0
Haemorrhoidal haemorrhage	1 (0.4)	0	0	0
Melaena	1 (0.4)	0	0	0
Subdural haematoma	1 (0.4)	0	0	0
Subdural haemorrhage	1 (0.4)	0	0	0
Subarachnoid haemorrhage	0	0	1 (0.7)	0
Serious bleeding for which a causal relationship to the study drug could not be ruled out	3 (1.2)	1 (0.4)	0	0
Gastrointestinal haemorrhage	1 (0.4)	1 (0.4)	0	0
Haematuria	1 (0.4)	0	0	0
Subdural haemorrhage	1 (0.4)	0	0	0
Bleeding leading to treatment discontinuation of any study drug[*3]	2 (0.8)	2 (0.8)	0	1 (0.7)
Bleeding leading to dose interruption of any study drug[*3]	8 (3.3)	3 (1.2)	9 (6.0)	3 (2.1)
Epistaxis	1 (0.4)	1 (0.4)	2 (1.3)	1 (0.7)
Gastrointestinal haemorrhage	0	1 (0.4)	2 (1.3)	1 (0.7)
Retinal haemorrhage	1 (0.4)	0	2 (1.3)	0
Bleeding leading to dose reduction of any study drug[*3]	1 (0.4)	0	1 (0.7)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in either belantamab mafodotin group; *3, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group. No bleeding led to treatment discontinuation or dose reduction of any study drug.

In the Japan expansion cohort in the DREAMM-7 study, there were no cases of bleeding leading to death and no serious cases of bleeding in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no cases of bleeding leading to death and no serious cases of bleeding in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, bleeding leading to death occurred in 3 subjects in the belantamab mafodotin group (1.4% total; subdural haematoma [2 subjects]; cerebral haemorrhage, and haemorrhagic stroke [1 subject each]; some patients were counted more than once), and a causal relationship to belantamab mafodotin was ruled out for all these events. Serious bleeding occurred in 12 subjects in the belantamab mafodotin group (5.5% total; subdural haematoma [3 subjects]; cerebral haemorrhage, gastrointestinal haemorrhage, and haematuria [2 subjects each]; epistaxis, gastric haemorrhage, haematochezia, haemorrhagic stroke, shock haemorrhagic, and small intestinal haemorrhage [1 subject each]; some patients were counted more than once). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for cerebral haemorrhage (1 subject).

Table 73 shows the details of patients who experienced serious bleeding for which a causal relationship to belantamab mafodotin could not be ruled out in DREAMM-3, DREAMM-7, and DREAMM-8 studies.

Table 73. List of patients who experienced serious bleeding for which a causal relationship to belantamab mafodotin could not be ruled out

Study	Age	Sex	PT	Grade	Onset day	Duration (days)	Treatment change*	Outcome
DREAMM-3	7[redacted]	M	Cerebral haemorrhage	4	256	19	Dose interruption/delay	Resolved (sequalae)
DREAMM-7	4[redacted]	M	Subdural haemorrhage	5	96	5	Treatment discontinuation	Death

*, Treatment of belantamab mafodotin (DREAMM-3 study) or any study drug (DREAMM-7 study)

PMDA's view:
The limited number of subjects who experienced serious bleeding in the DREAMM-3, DREAMM-7, and DREAMM-8 studies makes it difficult to determine conclusively as to whether belantamab mafodotin/Bd or belantamab mafodotin/Pd is associated with bleeding. However, given that there were reports of serious bleeding for which a causal relationship to belantamab mafodotin could not be ruled out, it was concluded that information on the incidence of bleeding in the clinical studies should be included in the package insert and other materials. In addition, the applicant should continue to collect post-marketing data on these events, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.7 ILD

The applicant's explanation about ILD associated with belantamab mafodotin:
To evaluate ILD-related adverse events, events classified as MedDRA SMQ "interstitial lung disease (narrow)" were collected.

The incidence of ILD across all the clinical studies submitted as evaluation data is summarized below. ILD-related adverse events were reported in the DREAMM-3, DREAMM-7, and DREAMM-8 studies.

In the DREAMM-7 study, ILD-related adverse events occurred in 2 subjects in the belantamab mafodotin/Bd group (0.8%; ILD in 2 subjects) and 1 subject in the DAR/Bd group (0.4%; radiation pneumonitis). A causal relationship to the study drug could not be ruled out for ILD (2 subjects) in the belantamab mafodotin/Bd group. Serious ILD occurred in 1 subject in the belantamab mafodotin/Bd group (0.4%; ILD), for which a causal relationship to the study drug could not be ruled out. ILD led to treatment discontinuation of the study drug in 1 subject in the belantamab mafodotin/Bd group (0.4%; ILD). There were no cases of ILD that led to death, or dose interruption or reduction of any study drug.

In the DREAMM-8 study, ILD-related adverse events occurred in 1 subject in the belantamab mafodotin/Pd group (0.7%; pneumonitis) and 4 subjects in the VPd group (2.8% total; bronchiolitis [2 subjects]; pneumonitis and ILD [1 subject each]). Among these events, a causal relationship to the study drug could not be ruled out for pneumonitis (1 subject) in the belantamab mafodotin/Pd group and bronchiolitis (2 subjects) in the VPd group. Serious ILD occurred in 1 subject in the belantamab mafodotin/Pd group (0.7%; pneumonitis) and 3 subjects (2.1% total; bronchiolitis [2 subjects] and ILD [1 subject]) in the VPd group. Among these, a causal relationship to the study drug could not be ruled out for pneumonitis (1 subject) in the belantamab mafodotin/Pd group and bronchiolitis (2 subjects) in the VPd group. ILD led to treatment discontinuation of the study drug in 1 subject in the belantamab mafodotin/Pd group (0.7%; pneumonitis), and ILD leading to dose interruption of any study drug in 1 subject in the belantamab mafodotin/Pd group (0.7%; pneumonitis) and 4 subjects in the VPd group (2.8% total; bronchiolitis [2 subjects]; pneumonitis and ILD [1 subject each]). There were no cases of ILD leading to death or dose reduction of any study drug.

In the Japan expansion cohort in the DREAMM-7 study, there were no cases of ILD leading to death and no serious cases of ILD in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no cases of ILD leading to death and no serious cases of ILD in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, ILD-related adverse events occurred in 3 subjects in the belantamab mafodotin group (1.4% total; pneumonitis [2 subjects] and ILD [1 subject]), and a causal relationship to the study drug could not be ruled out for all these events. Serious ILD occurred in 2 subjects in the belantamab mafodotin group (0.9%; pneumonitis). Among these, a causal relationship to the study drug could not be ruled out for pneumonitis in 1 subject. ILD leading to treatment discontinuation of any study drug occurred in the belantamab mafodotin group (1 subject, 0.5%; pneumonitis). ILD leading to dose interruption of any study drug occurred in the belantamab mafodotin group (3 subjects, 1.4%; pneumonitis [2 subjects] and ILD [1 subject]). There were no cases of ILD leading to death and no cases of ILD leading to dose reduction of any study drug.

In all clinical study data submitted as evaluation data, the details of patients who developed serious ILD for which a causal relationship to belantamab mafodotin could not be ruled out are shown in Table 74.

Table 74. List of patients who developed serious ILD for which a causal relationship to belantamab mafodotin could not be ruled out

Study	Age	Sex	PT	Grade	Onset day	Duration (days)	Treatment change*	Outcome
DREAMM-3	7[redacted]	M	Pneumonitis	3	233	8	Treatment discontinuation, dose interruption/delay	Resolved
DREAMM-7	6[redacted]	M	ILD	2	838	–	Treatment discontinuation	Not resolved

*, Treatment of belantamab mafodotin (DREAMM-3 study) or any study drug (DREAMM-7 study)

PMDA's view:

Based on the submitted data, the number of subjects who developed ILD in the clinical studies was limited, making it difficult to determine conclusively at this time as to whether belantamab mafodotin is associated with ILD. However, given factors including reports of serious ILD in the clinical studies for which a causal relationship to belantamab mafodotin could not be ruled out, it was concluded that information on the incidence of ILD in the clinical studies should be provided in an appropriate manner to healthcare professionals using the package insert and other materials. In addition, the applicant should continue to collect post-marketing data on these events, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.8 Second primary malignancies

The applicant's explanation about second primary malignancies associated with belantamab mafodotin:

To evaluate second primary malignancy-related adverse events, events classified under the MedDRA SMQ "malignant tumours" were collected.

Second primary malignancies reported in the DREAMM-7, DREAMM-8, and DREAMM-3 studies are summarized in the following paragraphs.

In the DREAMM-7 study, second primary malignancy-related adverse events occurred in 11 subjects in the belantamab mafodotin/Bd group (4.5% total; basal cell carcinoma [3 subjects]; papillary thyroid cancer, clear cell renal cell carcinoma, glioblastoma, intestinal adenocarcinoma, malignant melanoma, malignant neoplasm of conjunctiva, plasma cell myeloma, skin cancer, squamous cell carcinoma of skin, and transitional cell carcinoma [1 subject each]; some patients were counted more than once) and 7 subjects in the DAR/Bd group (2.8% total; basal cell carcinoma [3 subjects]; papillary thyroid cancer, keratoacanthoma, prostate cancer, and squamous cell carcinoma [1 subject each]). Among these events, a causal relationship to the study drug could not be ruled out for skin cancer and squamous cell carcinoma of skin (1 subject each) in the belantamab mafodotin/Bd group. Serious second primary malignancies occurred in 7 subjects in the belantamab mafodotin/Bd group (2.9% total; clear cell renal cell carcinoma, glioblastoma, intestinal adenocarcinoma, malignant neoplasm of conjunctiva, papillary thyroid cancer, skin cancer, and transitional cell carcinoma [1 subject each]), and a causal relationship

to the study drug was ruled out for all these events. Second primary malignancies leading to treatment discontinuation of any study drug occurred in 2 subjects in the belantamab mafodotin/Bd group (0.8% total; glioblastoma and intestinal adenocarcinoma [1 subject each]) and 1 subject in the DAR/Bd group (0.4%; prostate cancer).

In the DREAMM-8 study, second primary malignancy-related adverse events occurred in 6 subjects in the belantamab mafodotin/Pd group (4.0% total; basal cell carcinoma, lip squamous cell carcinoma, Bowen's disease, gallbladder adenocarcinoma, gastrointestinal cancer metastatic, gastrointestinal stromal tumour, transitional cell carcinoma [1 subject each]; some patients were counted more than once) and 5 subjects in the VPd group (3.4% total; squamous cell carcinoma of skin [2 subjects]; basal cell carcinoma, lip squamous cell carcinoma, colon cancer metastatic, glioma, plasma cell leukaemia, prostate cancer[1 subject each]; some patients were counted more than once). Among these events, a causal relationship to the study drug could not be ruled out for Bowen's disease and gastrointestinal cancer metastatic [1 subject each] in the belantamab mafodotin/Pd group, lip squamous cell carcinoma and prostate cancer (1 subject) in the VPd group. Second primary malignancies lead to death in 1 subject in the belantamab mafodotin/Pd group (0.7%; gastrointestinal cancer metastatic) and 1 subject in the VPd group (0.7%; colon cancer metastatic), and among these events, a causal relationship to the study drug could not be ruled out for gastrointestinal cancer metastatic (1 subject) in the belantamab mafodotin/Pd group. Serious second primary malignancies occurred in 4 subjects in the belantamab mafodotin/Pd group (2.7% total; gallbladder adenocarcinoma, gastrointestinal cancer metastatic, gastrointestinal stromal tumour, and transitional cell carcinoma [1 subject each]) and 2 subjects in the VPd group (1.4% total; colon cancer metastatic and glioma [1 subject each]). Among these events, a causal relationship to the study drug could not be ruled out for gastrointestinal cancer metastatic in the belantamab mafodotin/Pd group. Second primary malignancies led to treatment discontinuation of any study drug in 2 subjects in the belantamab mafodotin/Pd group (1.3% total; gallbladder adenocarcinoma and gastrointestinal cancer metastatic [1 subject each]) and 2 subjects in the VPd group (1.4% total; colon cancer metastatic and glioma [1 subject each]).

In the Japan expansion cohort in the DREAMM-7 study, no second primary malignancies led to death in the belantamab mafodotin/Bd group. Serious second primary malignancy occurred in 1 subject (10%, breast cancer), for which a causal relationship to the study drug could not be ruled out.

In the Japan expansion cohort in the DREAMM-8 study, there were no second primary malignancies leading to death and no serious second primary malignancies in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, second primary malignancy-related adverse events occurred in 10 subjects in the belantamab mafodotin group (4.6% total; malignant melanoma, plasma cell myeloma, and plasmacytoma [2 subjects each]; acute myeloid leukaemia, Bowen's disease, renal cell carcinoma, and transitional cell carcinoma [1 subject each]) and 5 subjects in the Pd group (acute myeloid leukaemia, Bowen's disease, breast cancer stage I, squamous cell carcinoma, and squamous cell carcinoma of skin

[1 subject each]). A causal relationship to the study drug was ruled out for all these events. Second primary malignancies led to death in 2 subjects in the belantamab mafodotin group (0.9% total; acute myeloid leukaemia and plasma cell myeloma [1 subject each]), and a causal relationship to the study drug was ruled out for both events. Serious second primary malignancies occurred in 6 subjects in the belantamab mafodotin group (2.8% total; plasma cell myeloma [2 subjects], acute myeloid leukaemia, malignant melanoma, renal cell carcinoma, and transitional cell carcinoma [1 subject each]) and 3 subjects in the Pd group (2.9% total; acute myeloid leukaemia, Bowen's disease, and breast cancer stage I [1 subject each]). A causal relationship to the study drug was ruled out for all these events. Second primary malignancies led to treatment discontinuation of any study drug in 1 subject in the belantamab mafodotin group (0.5%; acute myeloid leukaemia) and 2 subjects in the Pd group (2.0% total; acute myeloid leukaemia and breast cancer stage I [1 subject each]).

PMDA's view:
Based on the submitted data, the number of subjects who developed second primary malignancies in the clinical studies was limited, making it difficult to determine conclusively at this time as to whether belantamab mafodotin is associated with second primary malignancies. However, given that there were second primary malignancies for which a causal relationship to belantamab mafodotin could not be ruled out, it was concluded that information on the incidence of second primary malignancies in the clinical studies should be included in the package insert and other materials. In addition, the applicant should continue to collect post-marketing data on second primary malignancies, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.9 Infusion reaction

The applicant's explanation about the incidence of infusion reaction associated with belantamab mafodotin:
To evaluate infusion reaction, adverse events[83)] classified under 65 MedDRA PTs that occurred within 24 hours of the administration of belantamab mafodotin were collected. In the clinical studies, prophylaxis for infusion reaction was not mandatory, and the protocol specified that if infusion reaction occurred after the first or subsequent doses, then prophylaxis[84)] should be considered.

Table 75 and Table 76 show the incidence of infusion reaction in the DREAMM-7 and DREAMM-8 studies.

83) Abdominal pain, acute coronary syndrome, anaphylactic reaction, anaphylactoid reaction, angina pectoris, angioedema, asthenia, atrial flutter, back pain, bone pain, bradycardia, bronchospasm, cardio-respiratory arrest, chills, cough, cytokine release syndrome, diarrhoea, dizziness, dry mouth, dry throat, dyspnoea, extrasystoles, fatigue, feeling hot, flushing, gastrointestinal pain, headache, hyperhidrosis, hypersensitivity, hypertension, hypotension, hypoxia, infusion related reaction, laryngeal oedema, musculoskeletal chest pain, musculoskeletal pain, myocardial infarction, myocardial ischaemia, nausea, non-cardiac chest pain, oedema, oesophageal pain, oral pain, oropharyngeal pain, pain, pain in extremity, pain in jaw, pain of skin, palpitations, presyncope, proctalgia, pruritus, pyrexia, rash, sinus tachycardia, sinusitis, syncope, tachycardia, throat irritation, tremor, urticaria, ventricular extrasystoles, vomiting, wheezing, and drug hypersensitivity
84) No specific drugs were specified.

Table 75. Infusion reaction occurring in ≥5% of subjects in any group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction[*2]	5 (2.1)	0	48 (19.5)	6 (2.4)	11 (7.3)	2 (1.3)	0	0
Infusion related reaction	0	0	32 (13.0)	4 (1.6)	1 (0.7)	0	0	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 76. Incidence of serious infusion reaction, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Infusion reaction leading to death	0	0	0	0
Serious infusion reaction	0	5 (2.0)	0	0
Serious infusion reaction for which a causal relationship to the study drug could not be ruled out	0	5 (2.0)	0	0
Infusion reaction leading to treatment discontinuation of any study drug[*2]	0	1 (0.4)	1 (0.7)	0
Fatigue	0	0	1 (0.7)	0
Infusion reaction leading to dose interruption of any study drug[*3]	5 (2.1)	48 (19.5)	8 (5.3)	0
Asthenia	2 (0.8)	0	1 (0.7)	0
Infusion reaction leading to dose reduction of any study drug	0	1 (0.4)	1 (0.7)	0
Fatigue	0	1 (0.4)	1 (0.7)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in either belantamab mafodotin group; *3, adverse events occurring in ≥2 subjects in either belantamab mafodotin group

In the Japan expansion cohort in the DREAMM-7 study, there were no infusion reaction leading to death and no serious infusion reaction in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no infusion reaction leading to death and no serious infusion reaction in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, the incidence of infusion reaction was 18.0% (39 of 217 subjects) in the belantamab mafodotin group. Infusion reaction led to death in 1 subject in the belantamab mafodotin group (0.5%; cardio-respiratory arrest), and a causal relationship to belantamab mafodotin was ruled out. Serious infusion reaction occurred in 6 subjects in the belantamab mafodotin group (2.8% total; infusion related reaction [4 subjects]; cardio-respiratory arrest and cytokine release syndrome [1 subject each]). Among these, a causal relationship to belantamab mafodotin could not be ruled out for infusion related reaction (4 subjects) and cytokine release syndrome[85)] (1 subject).

85) The patient, a female aged 8[redacted] years, developed cytokine release syndrome (Grade 1) following administration of the first dose of belantamab mafodotin, with a duration of approximately 3 days. The outcome was reported as "resolved."

PMDA's view:

In the DREAMM-7 and DREAMM-8 studies, in which belantamab mafodotin was administered in the regimens (i.e., Bd and Pd) containing DEX, no serious infusion reaction occurred. Consequently, no cautionary statements on infusion reaction are necessary at present when belantamab mafodotin is administered in these regimens. However, in the DREAMM-3 study, which evaluated belantamab mafodotin monotherapy, infusion reaction occurred in some patients as well as serious infusion reaction for which a causal relationship to belantamab mafodotin could not be ruled out. It was therefore concluded that information on the incidence of infusion reaction following administration of belantamab mafodotin should be provided to healthcare professionals. In addition, the applicant should continue to collect post-marketing data on these events, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.10 Central nervous system disorders

The applicant's explanation about central nervous system disorders associated with belantamab mafodotin:

To evaluate central nervous system disorders, events classified as MedDRA SOC "nervous system disorders," excluding PTs classified as MedDRA SMQ "peripheral neuropathy (narrow)," were counted.

Table 77 and Table 78 show the incidence of central nervous system disorders in the DREAMM-7 and DREAMM-8 studies.

Table 77. Central nervous system disorders occurring in ≥5% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Central nervous system disorders[*2]	193 (79.8)	75 (31.0)	116 (47.2)	21 (8.5)	130 (86.7)	50 (33.3)	68 (46.9)	17 (11.7)
Vision blurred	160 (66.1)	53 (21.9)	26 (10.6)	2 (0.8)	119 (79.3)	26 (17.3)	22 (15.2)	0
Photophobia	114 (47.1)	5 (2.1)	6 (2.4)	0	66 (44.0)	5 (3.3)	6 (4.1)	0
Dizziness	21 (8.7)	1 (0.4)	19 (7.7)	0	9 (6.0)	1 (0.7)	17 (11.7)	2 (1.4)
Headache	21 (8.7)	0	18 (7.3)	0	9 (6.0)	0	8 (5.5)	0
Paraesthesia	14 (5.8)	0	13 (5.3)	0	4 (2.7)	0	5 (3.4)	0
Visual acuity reduced	14 (5.8)	4 (1.7)	5 (2.0)	1 (0.4)	34 (22.7)	20 (13.3)	8 (5.5)	1 (0.7)
Muscular weakness	7 (2.9)	0	5 (2.0)	0	13 (8.7)	0	8 (5.5)	2 (1.4)
Tremor	3 (1.2)	0	4 (1.6)	1 (0.4)	9 (6.0)	0	5 (3.4)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 78. Incidence of serious central nervous system disorders, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Central nervous system disorders leading to death[*2]	2 (0.8)	2 (0.8)	2 (1.3)	1 (0.7)
Cerebral haemorrhage	1 (0.4)	0	0	0
Subdural haemorrhage	1 (0.4)	0	0	0
Cerebral infarction	0	0	1 (0.7)	0
Meningoencephalitis herpetic	0	0	1 (0.7)	0
Central nervous system disorders leading to death for which a causal relationship to the study drug could not be ruled out	1 (0.4)	0	1 (0.7)	0
Subdural haemorrhage	1 (0.4)	0	0	0
Meningoencephalitis herpetic	0	0	1 (0.7)	0
Serious central nervous system disorders[*3]	15 (6.2)	11 (4.5)	12 (8.0)	7 (4.8)
Orthostatic hypotension	4 (1.7)	3 (1.2)	0	0
Syncope	4 (1.7)	1 (0.4)	1 (0.7)	0
Serious central nervous system disorders for which a causal relationship to the study drug could not be ruled out[*4]	7 (2.9)	4 (1.6)	1 (0.7)	1 (0.7)
Orthostatic hypotension	3 (1.2)	2 (0.8)	0	0
Syncope	2 (0.8)	0	0	0
Central nervous system disorders leading to treatment discontinuation of any study drug[*5]	9 (3.7)	4 (1.6)	5 (3.3)	5 (3.4)
Vision blurred	5 (2.1)	0	1 (0.7)	0
Central nervous system disorders leading to dose interruption of any study drug[*5]	100 (41.3)	19 (7.7)	83 (55.3)	15 (10.3)
Vision blurred	80 (33.1)	1 (0.4)	55 (36.7)	0
Photophobia	33 (13.6)	0	22 (14.7)	0
Orthostatic hypotension	5 (2.1)	2 (0.8)	0	0
Visual acuity reduced	7 (2.9)	0	26 (17.3)	0
Diplopia	3 (1.2)	0	3 (2.0)	0
Muscular weakness	1 (0.4)	0	5 (3.3)	4 (2.8)
Central nervous system disorders leading to dose reduction of any study drug[*5]	33 (13.6)	11 (4.5)	29 (19.3)	11 (7.6)
Vision blurred	27 (11.2)	2 (0.8)	3 (2.0)	0
Photophobia	5 (2.1)	0	0	0
Muscular weakness	2 (0.8)	1 (0.4)	11 (7.3)	6 (4.1)
Agitation	0	0	5 (3.3)	0
Tremor	0	1 (0.4)	5 (3.3)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively; *2, adverse events occurring in either belantamab mafodotin group; *3, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group; *4, among events listed under serious central nervous system disorders, events for which a causal relationship to the study drug could not be ruled out; *5, adverse events occurring in ≥2% of subjects in either belantamab mafodotin group.

In the Japan expansion cohort in the DREAMM-7 study, there were no central nervous system disorders leading to death and no serious central nervous system disorders in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no central nervous system disorders leading to death and no serious central nervous system disorders in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, central nervous system disorders led to death in 4 subjects in the belantamab mafodotin group (1.8% total; subdural haematoma [2 subjects]; cerebral haemorrhage, encephalopathy, and haemorrhagic stroke [1 subject each]; some patients were counted more than once), and a causal relationship to belantamab mafodotin was ruled out for all these events. Serious central nervous system disorders occurred in 18 subjects in the belantamab mafodotin group (8.3% total; subdural haematoma

and spinal cord compression [3 subjects each]; cerebral haemorrhage and encephalopathy [2 subjects each]; cauda equina syndrome, concussion, confusional state, epilepsy, haemorrhagic stroke, hyperammonaemic encephalopathy, neurological decompensation, radicular pain, spinal stenosis, transient global amnesia, and transient ischaemic attack [1 subject each]; some patients were counted more than once). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for cerebral haemorrhage, confusional state, and transient global amnesia (1 subject each).

Table 79 shows the details of patients who developed serious central nervous system disorders for which a causal relationship to belantamab mafodotin could not be ruled out in the DREAMM-3, DREAMM-7, and DREAMM-8 studies.

Table 79. List of patients who developed serious central nervous system disorders for which a causal relationship to belantamab mafodotin could not be ruled out

Study	Age	Sex	PT	Grade	Onset day	Duration (days)	Treatment change*	Outcome
DREAMM-3	7[redacted]	M	Cerebral haemorrhage	4	256	19	Dose interruption/delay	Resolved (with sequelae)
	8[redacted]	F	Confusional state	2	45	1	No change	Resolved
	5[redacted]	M	Transient global amnesia	1	84	4	No change	Resolved
DREAMM-7	7[redacted]	F	Herpes zoster	3	30	11	Dose interruption/delay	Resolved (with sequelae)
	4[redacted]	M	Subdural haemorrhage	5	96	5	Treatment discontinuation	Death

*, Treatment of belantamab mafodotin (DREAMM-3 study) or any study drug (DREAMM-7 study)

PMDA's view:

Among central nervous system disorders reported in the DREAMM-3, DREAMM-7, and DREAMM-8 studies, some events were also classified under such categories as eye disorders, infections, or bleeding-related adverse events. In addition, the limited number of patients who developed central nervous system disorders as well as other factors make it difficult to determine conclusively the risk of such events associated with belantamab mafodotin. Therefore, the applicant should continue to collect post-marketing data on central nervous system disorders, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.3.11 Peripheral nerve disorders

The applicant's explanation about peripheral nerve disorders associated with belantamab mafodotin:

To evaluate peripheral nerve disorder-related adverse events, events classified as MedDRA SMQ "peripheral neuropathy (narrow)" were counted.

Table 80 and Table 81 show the incidence of peripheral nerve disorders in the DREAMM-7 and DREAMM-8 studies.

Table 80. Incidence of peripheral nerve disorders occurring in ≥5% of subjects in either belantamab mafodotin group (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)							
	DREAMM-7				DREAMM-8			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246		Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Peripheral nerve disorders[*2]	124 (51.2)	10 (4.1)	121 (49.2)	15 (6.1)	19 (12.7)	1 (0.7)	60 (41.4)	5 (3.4)
Peripheral sensory neuropathy	61 (25.2)	2 (0.8)	51 (20.7)	1 (0.4)	5 (3.3)	0	15 (10.3)	1 (0.7)
Neuropathy peripheral	50 (20.7)	3 (1.2)	55 (22.4)	10 (4.1)	11 (7.3)	1 (0.7)	34 (23.4)	4 (2.8)
Polyneuropathy	15 (6.2)	3 (1.2)	13 (5.3)	4 (1.6)	3 (2.0)	0	6 (4.1)	0

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, total of adverse events that were to be included in the calculation

Table 81. Incidence of serious peripheral nerve disorders, etc. (DREAMM-7 and DREAMM-8 studies)

PT[*1]	Number of subjects (%)			
	DREAMM-7		DREAMM-8	
	Belantamab mafodotin/Bd N = 242	DAR/Bd N = 246	Belantamab mafodotin/Pd N = 150	VPd N = 145
Peripheral nerve disorders leading to death	0	0	0	0
Serious peripheral nerve disorders	0	0	0	0
Peripheral nerve disorders leading to treatment discontinuation of any study drug[*2]	26 (10.7)	24 (9.8)	2 (1.3)	2 (1.4)
Peripheral sensory neuropathy	13 (5.4)	6 (2.4)	0	1 (0.7)
Neuropathy peripheral	6 (2.5)	11 (4.5)	0	1 (0.7)
Polyneuropathy	7 (2.9)	5 (2.0)	0	0
Neuralgia	1 (0.4)	2 (0.8)	2 (1.3)	0
Peripheral nerve disorders leading to dose interruption of any study drug[*2]	45 (18.6)	35 (14.2)	5 (3.3)	22 (15.2)
Peripheral sensory neuropathy	25 (10.3)	15 (6.1)	1 (0.7)	4 (2.8)
Neuropathy peripheral	13 (5.4)	11 (4.5)	3 (2.0)	9 (6.2)
Neuralgia	5 (2.1)	6 (2.4)	1 (0.7)	5 (3.4)
Polyneuropathy	3 (1.2)	4 (1.6)	1 (0.7)	3 (2.1)
Peripheral nerve disorders leading to dose reduction of any study drug[*2]	68 (28.1)	77 (31.3)	5 (3.3)	42 (29.0)
Peripheral sensory neuropathy	33 (13.6)	31 (12.6)	0	10 (6.9)
Neuropathy peripheral	24 (9.9)	33 (13.4)	4 (2.7)	24 (16.6)
Polyneuropathy	9 (3.7)	8 (3.3)	1 (0.7)	4 (2.8)
Neuralgia	8 (3.3)	7 (2.8)	2 (1.3)	6 (4.1)

*1, Adverse events in the DREAMM-7 and DREAMM-8 studies are coded as per MedDRA ver.26.0 and ver.26.1, respectively;
*2, adverse events occurring in ≥1% of subjects in either belantamab mafodotin group

In the Japan expansion cohort in the DREAMM-7 study, there were no peripheral nerve disorders leading to death and no serious peripheral nerve disorders in the belantamab mafodotin/Bd group.

In the Japan expansion cohort in the DREAMM-8 study, there were no peripheral nerve disorders leading to death and no serious peripheral nerve disorders in the belantamab mafodotin/Pd group.

In the DREAMM-3 study, no peripheral nerve disorders led to death. A serious peripheral nerve disorder occurred in 1 subject in the belantamab mafodotin group (0.5%; peripheral motor neuropathy), for which a causal relationship to belantamab mafodotin was ruled out.

PMDA's view:

Although peripheral nerve disorders occurred in a certain proportion of patients in the DREAMM-7 study, these may be attributed to the effect of the co-administered drug (BOR[86]). In the DREAMM-8 and DREAMM-3 studies, which evaluated belantamab mafodotin/Pd and belantamab mafodotin monotherapy, respectively, serious peripheral nerve disorders occurred in a limited number of subjects, and a causal relationship to the study drug was ruled out. Given this and other factors, it is difficult to determine conclusively the risk of such events associated with belantamab mafodotin. Therefore, the applicant should continue to monitor the incidence of peripheral nerve disorders in the post-marketing setting, and any new information that becomes available should be provided to healthcare professionals in an appropriate manner.

7.R.4 Clinical positioning and indication

The proposed indication of belantamab mafodotin and the "Precautions Concerning Indication" section were as follows.

Indication	Precautions concerning indication
Relapsed or refractory multiple myeloma	• Eligible patients for belantamab mafodotin must have received at least 1 prior line of standard of care therapy, and MM is non-responsive to the therapy or relapsed after treatment. • Whether a patient is eligible for treatment with belantamab mafodotin should be decided by physicians who are fully familiar with prior therapy and other details of patients enrolled in the clinical studies presented in the "Clinical Studies" section, and have a thorough understanding of the efficacy and safety of belantamab mafodotin.

Based on the discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and in the following sections, PMDA concluded that it is appropriate to specify the indication of belantamab mafodotin and the "Precautions Concerning Indication" section as proposed by the applicant.

7.R.4.1 Clinical positioning and indication of belantamab mafodotin

In the established clinical practice guidelines[87] and textbooks[88] of hematology and clinical oncology published in Japan and other countries, no descriptions of belantamab mafodotin/Bd or belantamab mafodotin/Pd for the treatment of relapsed or refractory MM were found.

The applicant's explanation about the clinical positioning and indication of belantamab mafodotin/Bd and belantamab mafodotin/Pd:

The clinical practice guidelines published in Japan and other countries (Practical Guidelines for Hematological Malignancies 2024, edited by the Japanese Society of Hematology; NCCN Guidelines [v1.2025]) recommend multi-drug combination therapies as treatment options for relapsed or refractory

86) Peripheral nerve disorders are listed as clinically significant adverse drug reactions associated with BOR.

87) See the NCCN Guidelines (v1.2025), European Hematology Association (EHA)-ESMO Guidelines (*Ann Oncol.* 2021;32:309-22), and Practical Guidelines for Hematological Malignancies 2024 (Japanese Society of Hematology). The National Cancer Institute Physician Data Query (NCI-PDQ) (November 26, 2024 version) presented clinical data for the combination therapies targeting BCMA (belantamab mafodotin/Bd and belantamab mafodotin/Pd), and suggested that the use of BCMA-targeted therapy may be better than the standard of care.

88) See Williams Hematology (10th Edition) and Wintrobe's Clinical Hematology (15th Edition).

MM including the following: doublet regimens consisting of an immunomodulatory agent or a proteasome inhibitor, and DEX (Ld; Bd); triplet regimens consisting of an immunomodulatory agent, a proteasome inhibitor, and DEX (VPd; combination regimen consisting of carfilzomib, LEN, and DEX [CFZ/Ld]); triplet regimens consisting of an anti-CD38 monoclonal antibody, an immunomodulatory agent or a proteasome inhibitor, and DEX (DAR/Bd; DAR/Ld). In recent years, LEN is frequently used as a first-line therapy, and the use of DAR is also increasing; therefore, new treatment options following these therapies are needed.

Under the circumstances, results from the DREAMM-7 and DREAMM-8 studies, which were conducted in patients with relapsed or refractory MM, demonstrated the clinical utility of belantamab mafodotin/Bd and belantamab mafodotin/Pd [see Sections 7.R.1 and 7.R.2]. Therefore, it is considered that belantamab mafodotin/Bd and belantamab mafodotin/Pd can be positioned as treatment options for patients with relapsed or refractory MM.

Based on the above, the proposed indication of belantamab mafodotin was defined as "relapsed or refractory multiple myeloma." Given that in the DREAMM-7 and DREAMM-8 studies, patients with ≥1 prior regimen[89)] were eligible, information such as the prior treatments of patients enrolled in the DREAMM-7 and DREAMM-8 studies was included in the "Clinical Studies" section of the package insert, and the following precautions were included in the proposed "Precautions Concerning Indication" section.

Precautions Concerning Indication

- Eligible patients for belantamab mafodotin must have received at least 1 prior line of standard of care therapy, and MM is non-responsive to the therapy or relapsed after treatment.
- Whether a patient is eligible for treatment with belantamab mafodotin should be decided by physicians who are fully familiar with prior therapy and other details of patients enrolled in the clinical studies presented in the "Clinical Studies" section, and have a thorough understanding of the efficacy and safety of belantamab mafodotin.

It is expected that the following issues will be taken into consideration when selecting belantamab mafodotin/Bd or belantamab mafodotin/Pd.

- If MM relapsed at least 9 to 12 months after the last dose of the first line of anti-MM treatment, regimens containing the same class of agents as the first line (proteasome inhibitors or immunomodulatory agents) are recommended. Conversely, if MM relapsed within the above 9- to 12-month period, changing to a regimen containing other types of agents is recommended (Practical Guidelines for Hematological Malignancies 2024). Therefore, it is considered that belantamab mafodotin/Bd will be selected if an immunomodulatory agent was used in prior treatment and the patient experienced progression during treatment or early relapse.

89) Because VPd was recommended for patients with relapsed or refractory MM who had received prior LEN-containing therapy, patients with prior LEN-containing therapy were eligible in the DREAMM-8 study [see Section 7.R.2.1].

- For patients with MM refractory to LEN, POM-containing regimens are recommended as the subsequent therapy [see Section 7.R.2.1]; therefore, belantamab mafodotin/Pd is considered an appropriate choice.
- From a safety profile standpoint, given that the incidence of peripheral nerve disorders caused by BOR, the co-administered drug, tended to be higher in patients treated with belantamab mafodotin/Bd than in patients treated with belantamab mafodotin/Pd [see Section 7.R.3.11], it is considered appropriate to select belantamab mafodotin/Pd rather than belantamab mafodotin/Bd as the treatment for patients with peripheral nerve disorders.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

After the application was filed, the Dosage and Administration and the Precautions Concerning Dosage and Administration sections of belantamab mafodotin were revised as requested by the applicant, and the following were established.

Dosage and Administration	Precautions Concerning Dosage and Administration
In combination with bortezomib and dexamethasone The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose, administered as an intravenous infusion every 3 weeks. From the second dose onward, the dose should be reduced or withheld depending on the patient's condition. **In combination with pomalidomide and dexamethasone** The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second dose, administered as an intravenous infusion every 4 weeks. From the second dose onward, the dose should be reduced or withheld depending on the patient's condition.	• The antineoplastic agent to be co-administered with belantamab mafodotin should be used by physicians who are fully familiar with the details in the "Clinical Studies" section. • The diluted reconstituted solution of belantamab mafodotin should be administered as an intravenous infusion over at least 30 minutes. • For patients receiving belantamab mafodotin in combination with bortezomib and dexamethasone, belantamab mafodotin treatment should be continued after the end of the combination therapy. • Dose modification guidelines for adverse drug reactions associated with belantamab mafodotin • Specifications related to ophthalmologic examinations

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

Dosage and Administration	Precautions Concerning Dosage and Administration
In combination with bortezomib and dexamethasone: The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose, administered as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition. In combination with pomalidomide and dexamethasone: The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second dose, administered as an intravenous infusion over at least 30 minutes every 4 weeks. The dose should be reduced depending on the patient's condition.	• The antineoplastic agent to be co-administered with belantamab mafodotin should be used by physicians who are fully familiar with the details in the "Clinical Studies" section. • For patients receiving belantamab mafodotin in combination with bortezomib and dexamethasone, administration of belantamab mafodotin alone should be continued after the end of the combination therapy. • Dose modification guidelines for adverse drug reactions associated with belantamab mafodotin [see Section 7.R.5.2 for details] • Specifications related to ophthalmologic examinations [see Section 7.R.5.2 for details]

7.R.5.1 Dosage regimen of belantamab mafodotin

The following sections outline the applicant's explanation about the rationale for the selection of the dosage regimen of belantamab mafodotin. As described in Section "7.R.4.1 Clinical positioning and indication of belantamab mafodotin," multi-drug combination therapies are mainly used in the treatment of relapsed or refractory MM. Taking the circumstances into account, combination regimens were selected by combining belantamab mafodotin with an immunomodulatory drug or a proteasome inhibitor plus DEX (i.e., Bd and Pd).

(1) Belantamab mafodotin/Bd

Based on the evaluation described below, belantamab mafodotin 2.5 mg/kg Q3W was selected as the dosage regimen of belantamab mafodotin in the DREAMM-7 study. The results from the DREAMM-7 study demonstrated the clinical utility of belantamab mafodotin/Bd in the treatment of relapsed or refractory MM [see Sections 7.R.2 and 7.R.3]; therefore, the proposed dosage regimen for the combination therapy of belantamab mafodotin with Bd was selected.

- In the DREAMM-1 study, tolerability was investigated at different dose levels of belantamab mafodotin. Although no DLTs were detected up to 4.60 mg/kg Q3W, the highest dose level studied, tolerability tended to be poor, with persistent fever, headache, etc. at 4.60 mg/kg. Conversely, 3.40 mg/kg Q3W tended to exhibit a favorable safety profile. All subjects treated with 3.40 mg/kg Q3W achieved a response.
- In the DREAMM-2 study, belantamab mafodotin 2.5 and 3.4 mg/kg Q3W were compared. The results showed comparable efficacy (the proportion of subjects achieving VGPR or better response among subjects achieving a response was 60.0% and 58.8% at 2.5 and 3.4 mg/kg Q3W, respectively), while the safety data showed that the incidence of adverse events leading to death, dose reduction, dose interruption, or serious adverse events tended to be lower in the 2.5 mg/kg Q3W group.[90)]
- In the DREAMM-6 study, which evaluated belantamab mafodotin/Bd, belantamab mafodotin was administered by combining dose levels 1.9, 2.5, and 3.4 mg/kg and different administration methods. The efficacy data showed greater effectiveness at ≥2.5 mg/kg (VGPR or better response was the highest [67%] at 2.5 mg/kg Q3W) [see Section 7.1.3.2], while the safety data showed insignificant differences among the dose levels in terms of the incidence of adverse events [see Section 7.3.6]. Therefore, for combination therapy with Bd, 2.5 mg/kg Q3W was determined to be optimal. In the DREAMM-6 study, of the 15 subjects treated with 2.5 mg/kg Q3W, 2 subjects underwent dose reduction/interruption in Cycle 2, and 4 subjects underwent dose interruption in Cycle 3.

(2) Belantamab mafodotin/Pd

90) At belantamab mafodotin 2.5 or 3.4 mg/kg, the incidence of adverse events leading to death was 3% and 7%, respectively; serious adverse events, 40% and 47%, respectively; adverse events leading to dose reduction of the study drug, 29% and 41%, respectively; adverse events leading to dose interruption of the study drug, 54% and 62%, respectively.

Based on the evaluation described below, belantamab mafodotin 2.5 mg/kg for the first dose and 1.9 mg/kg Q4W for subsequent cycles were selected as the dosage regimen of belantamab mafodotin in the DREAMM-8 study. The results from the DREAMM-8 study demonstrated the clinical utility of belantamab mafodotin/Pd in the treatment of relapsed or refractory MM [see Sections 7.R.2 and 7.R.3]; therefore, the proposed dosage regimen for the combination therapy of belantamab mafodotin with Pd was selected.

- Based on the results from the DREAMM-1 and DREAMM-2 studies shown above in (1), an initial dose level of 2.5 mg/kg was selected for belantamab mafodotin, and a dosing interval of Q4W was selected based on the dosing schedule of Q4W for the combination therapy with POM and DEX.
- An investigator-initiated trial (ALGONQUIN study; *Nat Med.* 2024;30:543-51) was conducted outside Japan to evaluate belantamab mafodotin/Pd. Preliminary efficacy and safety results from the belantamab mafodotin 1.92 mg/kg Q4W and 2.5 mg/kg Q4W cohorts in the study showed that the starting dose of 2.5 mg/kg Q4W tended to be more effective compared to 1.92 mg/kg Q4W, while the incidence of adverse events including corneal events was lower in the 1.92 mg/kg Q4W cohort, indicating a favorable safety profile. In addition, in the 2.5 mg/kg Q4W cohort, all subjects underwent dose reduction or interruption of belantamab mafodotin in Cycle 2 or later. Therefore, taking these results into account, 2.5 mg/kg for the first dose and 1.9 mg/kg for the second and subsequent doses were selected.

In both belantamab mafodotin/Bd and belantamab mafodotin/Pd regimens, dose interruption of belantamab mafodotin occurred frequently.[91)] In addition, since there were reports that the dosing intervals after the second dose tended to be prolonged over time,[92)] it is considered appropriate to reduce the dose depending on the patient's condition. Therefore, "for the second and subsequent doses, the dose should be reduced or withheld depending on the patient's condition" was clearly stated in the Dosage and Administration section.

Taking the following issues into account, appropriate cautionary statements will be included in the Precautions Concerning Dosage and Administration section.

- A cautionary statement will be included to the effect that the antineoplastic agent to be co-administered with belantamab mafodotin should be used by physicians who are fully familiar with the details in the "Clinical Studies" section to ensure that belantamab mafodotin should only be used by physicians who have an adequate understanding of the dosing regimen of the antineoplastic agent that is to be co-administered.
- In the clinical studies, belantamab mafodotin was administered over at least 30 minutes. A cautionary statement regarding the infusion rate of belantamab mafodotin will be included.

91) In the DREAMM-7 and DREAMM-8 studies, the percentage of patients who underwent dose interruption was 88% (213 of 242 subjects) and 90% (135 of 150 subjects), respectively.
92) An additional analysis for the DREAMM-7 and DREAMM-8 studies showed that the dosing interval gradually extended from the start of treatment of belantamab mafodotin (3 and 4 weeks, respectively), and the median interval at 2 years was 12 and 16 weeks, respectively (International Myeloma Society Annual Meeting, September 2024).

- In the belantamab mafodotin/Bd regimen, administration of Bd continues up to Cycle 8, and belantamab mafodotin will be administered alone from Cycle 9 onward. Therefore, a cautionary statement will be included to ensure that this measure is implemented properly.

PMDA's view:

The applicant's explanation was generally acceptable. Regarding the situation of dose interruption, etc. of belantamab mafodotin in the clinical studies mentioned in (1), provision of information to healthcare professionals using educational materials will be sufficient, and it is not necessary to explicitly include it in the Dosage and Administration section. Conversely, the administration rate of belantamab mafodotin mentioned in (2) should be clearly stated in the Dosage and Administration section. Therefore, PMDA concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration sections should be established as shown in the table below.

Dosage and Administration	Precautions Concerning Dosage and Administration
In combination with bortezomib and dexamethasone: The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose, administered as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition. In combination with pomalidomide and dexamethasone: The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second and subsequent doses, administered as an intravenous infusion over at least 30 minutes every 4 weeks. The dose should be reduced depending on the patient's condition.	• The antineoplastic agent to be co-administered with belantamab mafodotin should be used by physicians who are fully familiar with the details in the "Clinical Studies" section. • For patients receiving belantamab mafodotin in combination with bortezomib and dexamethasone, administration of belantamab mafodotin alone should be continued after the end of the combination therapy.

7.R.5.2 Dose modification of belantamab mafodotin

The applicant's explanation about the dose modification of belantamab mafodotin for adverse drug reactions:

In the DREAMM-7 and DREAMM-8 studies, guidelines for dose interruption/reduction and treatment discontinuation of belantamab mafodotin for adverse drug reactions were established. Patients were able to tolerate belantamab mafodotin by complying with these guidelines. Accordingly, the dose modification guidelines were established in the Precautions Concerning Dosage and Administration section based on the setting of these studies with the following changes. In the DREAMM-8 study, which started after the DREAMM-7 study, more clinical data including data from the DREAMM-7 study were available at the time the study was designed, and therefore, it was considered possible to reduce the dose by 1 level lower than that specified in the DREAMM-7 study and/or to extend the dosing interval. As a result, the dose reduction levels of belantamab mafodotin for adverse drug reactions and the dosing intervals in the DREAMM-8 study, which evaluated belantamab mafodotin/Pd, differed from those in the DREAMM-7 study, which evaluated belantamab mafodotin/Bd.

- The guidelines for corneal examination findings and vision changes based on the KVA scale in the clinical studies were established [see Section 7.R.3.2]. However, the protocol for the DREAMM-8

study specified that if Grade 2 or 3 findings per the KVA scale were noted, after resolution to Grade ≤1, belantamab mafodotin treatment was to be resumed at a lower dose (1 level). Conversely, in the DREAMM-7 study, if Grade 3 findings per the KVA scale were noted, belantamab mafodotin treatment was to be resumed at a lower dose (1 level). For the package insert, the guidelines were conservatively set based on those in the DREAMM-8 study.

- For other adverse drug reactions (other than corneal examination findings and vision change, platelet count decreased, and infusion reaction), guidelines for actions (e.g., dose interruption) for Grade 2 adverse drug reactions were specified in the DREAMM-7 and DREAMM-8 studies. However, given that changing the dose of belantamab mafodotin was not mandatory when Grade 2 events occurred, and was left to the discretion of the investigator, it was determined that in clinical settings, physicians who are versed in the treatment of hematopoietic malignancies can make such decisions while taking the patient's condition into consideration. Therefore, the package insert only specifies actions to be taken for Grade 3 or 4 adverse drug reactions. In the DREAMM-7 study, when Grade 3 adverse drug reactions occurred, treatment was to be resumed at the same dose level. However, because treatment should be resumed more cautiously, it was decided that the package insert will include a statement recommending a one-level dose reduction if the above adverse drug reactions occur at belantamab mafodotin 2.5 mg/kg.
- For neutropenia, febrile neutropenia, and pneumonitis, given the circumstances for each adverse drug reaction, it was determined that in clinical settings, physicians who are versed in the treatment of hematopoietic malignancies can make decisions at their own discretion while taking the patient's condition into consideration; therefore, cautionary statements are to be included in the package insert to the effect that appropriate measures such as treatment discontinuation should be taken if abnormalities are noted. Therefore, no specific dose modification guidelines were established for these adverse drug reactions. In addition, dose modification guidelines are specified for Grade ≥3 "other adverse drug reactions"; therefore, these adverse drug reactions will also be handled appropriately based on the guidelines.
  - The incidence of neutropenia and febrile neutropenia was not high[93)] in the DREAMM-7 study, and no events led to treatment discontinuation. In the DREAMM-8 study, neutropenia occurred in 63% of patients; however, there was also a possibility that POM, the co-administered drug, could have affected the incidence of these events. No events led to treatment discontinuation.
  - Regarding pneumonitis, the incidence of pneumonitis and ILD was not high[94)] in the clinical studies, and no Japanese patients developed these events.

In the DREAMM-7 study, if Grade 4 "corneal examination findings and visual acuity" occur, treatment discontinuation of belantamab mafodotin should be considered, or restarting treatment with belantamab

93) The incidence of neutropenia-related events (e.g., febrile neutropenia, neutropenia, and neutrophil count decreased) was 18% (for any grade) and 9% (for Grade ≥3).
94) Pneumonitis did not occur in the DREAMM-7 study, and occurred in 1 patient in the DREAMM-8 study (Grade 3, serious; this event was determined to be related to POM only).

mafodotin (reduced dose) was allowed after the occurrence of a Grade 4 event depending on the patient's condition. In the DREAMM-8 study, after dose interruption, restarting treatment with belantamab mafodotin (reduced dose) after the occurrence of a Grade 4 event was allowed depending on the patient's condition. In the DREAMM-7 study, of 44 patients who developed Grade 4 corneal disorders, 31 patients (70%) resumed belantamab mafodotin after resolution of the events, while in the DREAMM-8 study, of 11 patients who developed Grade 4 corneal disorders, 8 patients (73%) resumed belantamab mafodotin after resolution of the events. Among patients who resumed belantamab mafodotin treatment, Grade ≥2 eye disorders occurred in 29 of 31 patients (94%) and 8 of 8 patients (100%) in the DREAMM-7 and DREAMM-8 studies, respectively. However, given that belantamab mafodotin-induced eye disorders are reversible, a cautionary statement will be included in the package insert to the effect that if Grade 4 "corneal examination findings and visual acuity" occur, withhold the dose until resolution, and after the event has resolved, resume treatment at a reduced dose.

The proposed dose modification guidelines for adverse drug reactions were established as described above.

PMDA's view:
The applicant's explanation was generally acceptable. However, given that the majority of patients who had presented with Grade 4 corneal findings and vision change and resumed belantamab mafodotin after resolution experienced relapse of Grade ≥2 eye disorders in the DREAMM-7 and DREAMM-8 studies, PMDA concluded that belantamab mafodotin should be discontinued if Grade 4 corneal findings and vision change occur.

Based on the above, it was concluded that the dose modification guidelines of belantamab mafodotin for adverse drug reactions should be established as shown below.

Precautions Concerning Dosage and Administration
If the patient develops an adverse drug reaction following administration of belantamab mafodotin, the dose of belantamab mafodotin must be interrupted, reduced, or treatment must be discontinued based on the following guidelines.

Dose levels for reductions

	Belantamab mafodotin/Bd	Belantamab mafodotin/Pd
Usual dose	2.5 mg/kg every 3 weeks	2.5 mg/kg for the first dose. For the second and subsequent doses, 1.9 mg/kg every 4 weeks
Dose reduction by 1 level	1.9 mg/kg every 3 weeks	1.9 mg/kg every 8 weeks
Dose reduction by 2 levels	Not applicable	1.4 mg/kg every 8 weeks

Dose interruption, reduction, and treatment discontinuation guidelines for adverse drug reactions

Adverse drug reaction	Severity[Note 1)]	Action
Corneal examination findings and vision change[Note 2)]	Grade 1: Corneal examination findings Mild[Note 3)] superficial punctate keratopathy (documented worsening from baseline, with or without symptoms) Change in BCVA See Grade 1 in the table below.	Continue treatment
	Grade 2: Corneal examination findings Moderate[Note 3)] superficial punctate keratopathy, patchy microcyst-like deposits, peripheral sub-epithelial haze, or a new peripheral stromal opacity Change in BCVA See Grade 2 in the table below.	Withhold treatment until both corneal examination findings and BCVA resolve to Grade ≤1. After resolution, resume treatment at a dose reduced by 1 level.[Note 4)]
	Grade 3: Corneal examination findings Severe[Note 3)] superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, central sub-epithelial haze, or a new central corneal stromal opacity Change in BCVA See Grade 3 in the table below.	
	Grade 4: Corneal examination findings Corneal epithelium defect Change in BCVA See Grade 4 in the table below.	Discontinue treatment.
Platelet count decreased	Grade 3	Without bleeding: • At 2.5 mg/kg: reduce the dose to 1.9 mg/kg, and continue treatment.[Note 5)] • At ≤1.9 mg/kg: continue treatment at the same dose level.[Note 5)] With bleeding: • Withhold treatment until resolution to Grade ≤2. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Withhold treatment until resolution to Grade ≤3. Consider resuming treatment only if there is no bleeding after resolution: • At 2.5 mg/kg: resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: resume treatment at the pre-interruption dose level. • If platelet count decreased is considered to be related to multiple myeloma, without bleeding, and resolves with transfusion to 25,000/μL, treatment may be resumed at the pre-interruption dose level.
Infusion reaction	Grade 2	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume at a reduced infusion rate (no more than half the rate at which the symptoms initially appeared). Consider prophylactic medication when resuming infusion and for subsequent infusions.

	Grade 3	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume infusion at a rate 1/4 to 1/8 of the rate at which the symptoms initially appeared. Consider prophylactic medication when resuming infusion. For subsequent infusions, prophylactic medication should be administered.
	Grade 4	Discontinue treatment.
Other adverse drug reactions	Grade 3	Withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Consider treatment discontinuation. If treatment is to be continued, withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.

Note 1) With the exception of corneal examination findings and vision change, adverse drug reactions were graded according to CTCAE v. 5.0.
Note 2) Examination results may differ between the left and right eyes. The severity should be determined based on the most severe corneal findings or vision change in either eye.
Note 3) For the assessment of superficial punctate keratopathy, see the relevant materials provided by the marketing authorization holder.
Note 4) For combination therapy with POM and DEX: if an adverse drug reaction occurs before the second dose, 1.9 mg/kg should be administered every 4 weeks from the second dose onward.
Note 5) For combination therapy with BOR and DEX: if the decreased platelet count resolves to Grade ≤2, the original dose level may be used.

Severity of change in BCVA due to eye disorder

Baseline BCVA	Grade 1	Grade 2	Grade 3	Grade 4
1.5	1.2	0.8-1.0	0.1-0.7	<0.1
1.2	1.0	0.6-0.9	0.1-0.5	<0.1
1.0	0.8-0.9	0.5-0.7	0.1-0.4	<0.1
0.9	0.6-0.8	0.4-0.5	0.1-0.3	<0.1
0.8	0.6-0.7	0.4-0.5	0.1-0.3	<0.1
0.7	0.5-0.6	0.3-0.4	0.1-0.2	<0.1
0.6	0.5	0.3-0.4	0.1-0.2	<0.1
0.5	0.4	0.3	0.1-0.2	<0.1
0.4	0.3	0.2	0.1	<0.1
0.3	—	0.2	0.1	<0.1
0.2	—	0.1	—	<0.1

7.R.5.3 Dose modification based on ophthalmologic examinations

The applicant considers that when belantamab mafodotin is administered, ophthalmologic examinations should be performed on a regular basis, and the dose of belantamab mafodotin should be modified based on the results [see Section 7.R.5.2]. The following statement regarding ophthalmologic examination has been included in the proposed Precautions Concerning Dosage and Administration section.

- Ophthalmologic examinations (corneal examination findings and vision change) should be performed before each of the first 4 doses of belantamab mafodotin, and on an as-needed basis thereafter, and the results should be confirmed to assess the severity and determine the dose level, taking ocular symptoms into account. Because examination results may differ between the left and right eyes, the severity should be determined based on the most severe corneal findings or vision change in either eye. If any vision change is noted, its association with belantamab mafodotin should be clarified. If the dose of belantamab mafodotin is reduced due to corneal findings or vision change, the dose should not be re-escalated.

The applicant's explanation about the rationale for examination frequency above (first dose to fourth dose are mandatory and on an as-needed basis thereafter):

Protocol for the DREAMM-7 and DREAMM-8 studies specified that "ophthalmologic examinations should be performed before each of the first 6 doses of belantamab mafodotin." However, in the pooled analyses of data from the DREAMM-7 and DREAMM-8 studies, corneal events occurred in 92% of patients, and in 89% of these patients, the first corneal events occurred within the first 4 cycles. The median time to the first onset of Grade ≥2 corneal disorders that required dose modification was 58.0 and 57.0 days in the DREAMM-7 and DREAMM-8 studies, respectively. In addition, the relationship between the incidence of Grade ≥2 corneal events and cumulative number of belantamab mafodotin doses (Figure 10) also shows that the cumulative incidence of corneal events after the fourth dose of belantamab mafodotin is generally constant.

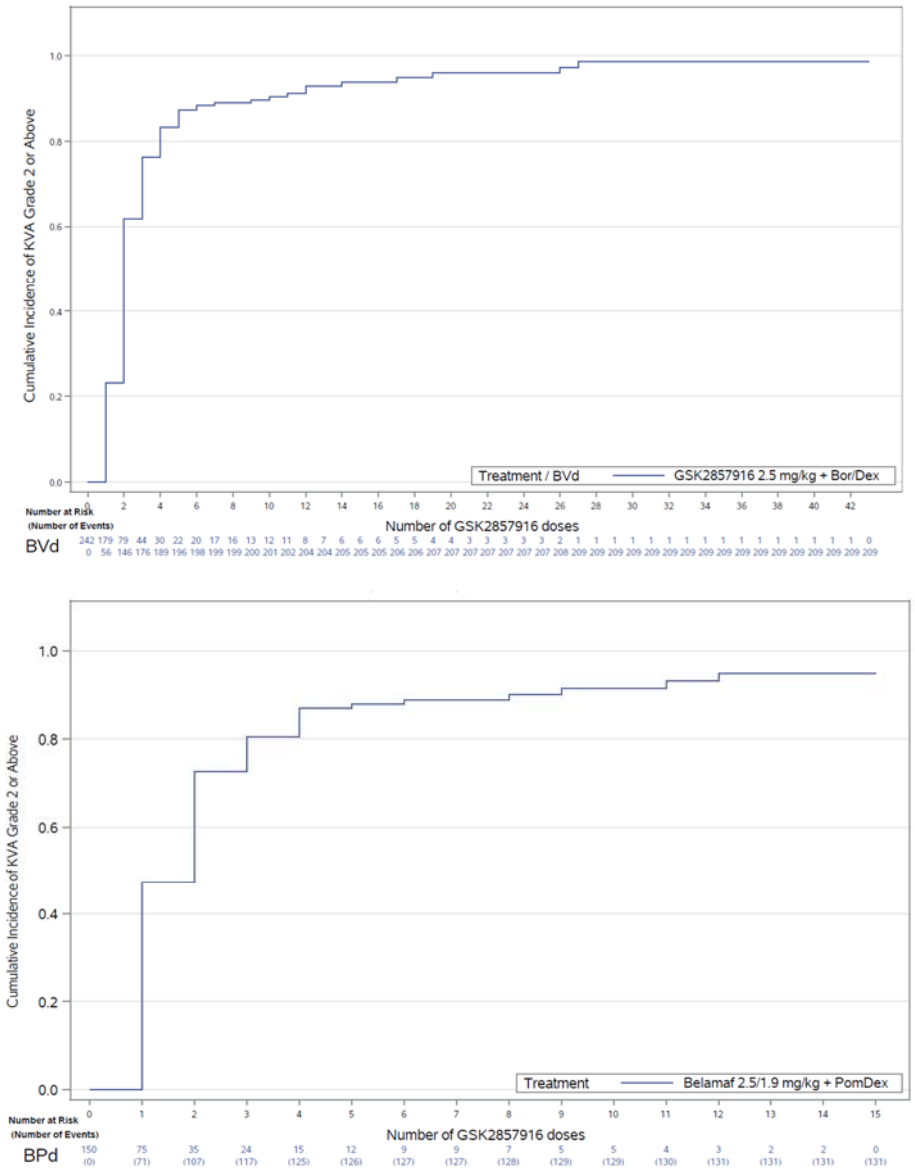

Figure 10. Cumulative number of belantamab mafodotin doses up to the onset of Grade ≥2 corneal events (DREAMM-7 study [top] and DREAMM-8 study [bottom])

Based on the above results, ophthalmologic examinations should always be performed before each of the first through fourth doses of belantamab mafodotin. Thereafter, ophthalmologic examinations before subsequent doses can be conducted as necessary depending on the patient's condition. It is considered that corneal events can be managed, and this statement will be included in the package insert.

PMDA accepted the applicant's explanation.

7.R.6 Risk management plan (draft)

The risk management plan for belantamab mafodotin will be formulated in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No.0411-1 and PFSB/ELD Notification No.0411-2, dated April 11, 2012) and "Risk Management Plan Templates, Instructions, and Publication" (PSEHB/PED Notification No. 0318-2 and PSEHB/PSD Notification No. 0318-1, dated March 18, 2022).

In view of the discussions presented in Section "7.R.3 Safety," PMDA has concluded that the risk management plan (draft) for belantamab mafodotin should include the safety and efficacy specifications presented in Table 82.

Table 82. Safety specification in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Eye disorders • Cytopenia • Infections	• Gastrointestinal disorders • Bleeding • ILD • Second primary malignancies • Infusion reaction	None
Efficacy specification		
None		

Based on the incidence and other aspects of eye disorders in the clinical studies [see Section 7.R.3.2], the applicant explained the safety measures for eye disorders associated with belantamab mafodotin as follows:

Given the risk of belantamab mafodotin-induced eye disorders, belantamab mafodotin should only be used at a medical institution capable of providing adequate medical care in collaboration with an ophthalmologist. In addition, the prescribing physician needs to be thoroughly familiar with the risk of belantamab mafodotin-associated eye disorders as well as the prevention and management measures specified in the package insert in order to minimize the risk of these disorders. Furthermore, information on eye disorder prevention and management measures will be provided to healthcare professionals (prescribing physicians and ophthalmologists), and educational materials for patients will also be provided. Accordingly, the following requirements are to be established as additional risk minimization activities.

- If it is difficult to perform ophthalmologic examinations at the medical institution where belantamab mafodotin is prescribed, a collaborating medical institution capable of performing such ophthalmologic examinations should be specified.
- The representative of the prescribing medical institution must consent to the prescribing physician receiving information on proper use.

PMDA accepted the applicant's explanation and concluded that appropriate measures should be taken based on the above statements.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing investigations:

The applicant plans to conduct a post-marketing surveillance covering all patients who will be receiving belantamab mafodotin to investigate the safety and other aspects of belantamab mafodotin in clinical use.

Based on the incidence of adverse events in the DREAMM-7 and DREAMM-8 studies, "corneal examination findings that may cause changes in vision (e.g., keratopathy)" have been identified as adverse events of special interest when belantamab mafodotin is administered and were included in the proposed safety specification for the surveillance.

A planned sample size of 200 patients and a follow-up period of 1 year from the start of treatment were proposed taking into account data from the DREAMM-7 and DREAMM-8 studies on the incidence and timing of onset of the events that are to be included in the safety specification for this surveillance.

PMDA's view:

Based on the discussions shown below and in Section "7.R.3 Safety," post-marketing surveillance should be conducted to evaluate the risk of adverse events of special interest when belantamab mafodotin is administered, in particular, gastrointestinal disorders, bleeding, and infusion reaction, while specifying these events in the safety specification for the surveillance. Among items included in the proposed safety specification for this surveillance, the relationship between eye disorders (e.g., keratopathy) caused by belantamab mafodotin and changes in vision has already been evaluated to some extent based on the currently available result data from the clinical studies. Therefore, it is not necessary to specify "corneal examination findings that may cause changes in vision (e.g., keratopathy)" as the primary evaluation objective. Rather, it is considered more appropriate to include it as a secondary evaluation item, with particular attention to the potential for irreversible effects on vision.

- While serious gastrointestinal disorders for which a causal relationship to belantamab mafodotin could not be ruled out have been reported, it was difficult to determine conclusively as to whether the events were associated with belantamab mafodotin based on the currently available data. Therefore, the risk of developing gastrointestinal disorders by organ should be investigated further.

- While serious bleeding events for which a causal relationship to belantamab mafodotin could not be ruled out have been reported, it was difficult to determine conclusively as to whether these events were associated with belantamab mafodotin based on the currently available data. Therefore, the risk of developing bleeding events by cause (in particular, with or without platelet count decreased) should be investigated further.
- Although no serious infusion reaction was reported when belantamab mafodotin was administered in combination with Bd and Pd in the DREAMM-7 and DREAMM-8 studies, respectively, serious infusion reaction for which a causal relationship to belantamab mafodotin could not be ruled out occurred in belantamab mafodotin monotherapy. Because infusion reaction may occur when belantamab mafodotin is administered, the risk of developing infusion reaction associated with belantamab mafodotin should be investigated further in clinical settings.

However, clinical trial results have already provided a certain level of knowledge on the safety of belantamab mafodotin, and no concerns have been identified that require clarification through a post-marketing all-case survey in Japan. Given these and other factors, PMDA concluded that it is unnecessary to conduct an all-case post-marketing surveillance.

Accordingly, PMDA concluded that the applicant should re-examine the target sample size and the duration of the follow-up period for the survey taking into account the incidence and onset timing of gastrointestinal disorders, bleeding events, and infusion reaction reported in the clinical studies.

7.3 Adverse events and other findings observed in clinical studies

The following sections discuss the main adverse events from the results of clinical studies submitted for safety evaluation, except for those that resulted in death, which are discussed in Sections "7.1 Evaluation data" and "7.2 Reference data."

7.3.1 Japanese phase I study (DREAMM-11 study)

7.3.1.1 Part 1

Any adverse events as well as adverse events for which a causal relationship to belantamab mafodotin could not be ruled out occurred in 4 of 4 subjects (100%) in the 2.5 mg/kg group and 4 of 4 subjects (100%) in the 3.4 mg/kg group. Adverse events occurring in ≥2 subjects in each group were platelet count decreased (4 subjects, 100%); leukopenia, ALT increased, AST increased, and infusion related reaction (2 subjects [50.0%] each) in the 2.5 mg/kg group; and thrombocytopenia, diarrhoea, enterocolitis, and headache (2 subjects [50.0%] each) in the 3.4 mg/kg group.

Serious adverse events occurred only in the 2.5 mg/kg group (2 of 4 subjects, 50.0%). There were no serious adverse events reported in ≥2 subjects in either group.

Adverse events led to treatment discontinuation of belantamab mafodotin in 1 of 4 subjects (25.0%) in the 2.5 mg/kg group, while no adverse events led to treatment discontinuation in the 3.4 mg/kg group.

There were no adverse events leading to treatment discontinuation of belantamab mafodotin in ≥2 subjects in either group.

7.3.1.2 Part 2

Any adverse events as well as adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 3 subjects (100%) in Part 2A (belantamab mafodotin/Bd) and in 4 of 4 subjects (100%) in Part 2B (belantamab mafodotin/Pd). Adverse events occurring in ≥2 subjects in each arm were thrombocytopenia (3 subjects, 100%); lymphopenia, diarrhoea, peripheral sensory neuropathy, and insomnia (2 subjects [66.7%] each) in Part 2A and thrombocytopenia, constipation, oedema peripheral, neutrophil count decreased, and platelet count decreased (2 subjects [50.0%] each) in Part 2B.

Serious adverse events occurred in 1 of 4 subjects (25.0%) in Part 2B, and no serious adverse events occurred in Part 2A. A serious adverse event (COVID-19) occurred in 1 subject and a causal relationship to the study drug was ruled out.

Adverse events led to treatment discontinuation in 2 of 4 subjects (50.0%) in Part 2B, and no adverse events led to treatment discontinuation in Part 2A. Adverse events that led to treatment discontinuation of the study drug were liver injury and neutrophil count decreased (1 subject [25.0%] each). A causal relationship to the study drug could not be ruled out for either event.

7.3.2 Global phase III study (DREAMM-7 study)

7.3.2.1 Main cohort

Adverse events occurred in all subjects, and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 242 of 242 subjects (100%) in the belantamab mafodotin/Bd group and 234 of 246 subjects (95.1%) in the DAR/Bd group. Table 83 shows adverse events occurring in ≥10% of subjects in either group.

Table 83. Adverse events occurring in ≥10% of subjects in either group

SOC PT (MedDRA/J ver.26.0)	Number of subjects (%)			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	242 (100)	230 (95.0)	246 (100)	192 (78.0)
Blood and lymphatic system disorders				
Thrombocytopenia	167 (69.0)	134 (55.4)	122 (49.6)	87 (35.4)
Anaemia	46 (19.0)	20 (8.3)	65 (26.4)	25 (10.2)
Neutropenia	34 (14.0)	30 (12.4)	27 (11.0)	15 (6.1)
Infections and infestations				
COVID-19	58 (24.0)	14 (5.8)	49 (19.9)	11 (4.5)
Upper respiratory tract infection	48 (19.8)	0	49 (19.9)	0
Pneumonia	44 (18.2)	28 (11.6)	22 (8.9)	10 (4.1)
Nervous system disorders				
Peripheral sensory neuropathy	61 (25.2)	2 (0.8)	51 (20.7)	1 (0.4)
Neuropathy peripheral	50 (20.7)	3 (1.2)	55 (22.4)	10 (4.1)
Gastrointestinal disorders				

SOC PT (MedDRA/J ver.26.0)	Number of subjects (%)			
	Belantamab mafodotin/Bd N = 242		DAR/Bd N = 246	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	78 (32.2)	9 (3.7)	77 (31.3)	10 (4.1)
Constipation	46 (19.0)	2 (0.8)	56 (22.8)	1 (0.4)
Nausea	39 (16.1)	2 (0.8)	30 (12.2)	0
Eye disorders				
Vision blurred	160 (66.1)	53 (21.9)	26 (10.6)	2 (0.8)
Dry eye	123 (50.8)	17 (7.0)	17 (6.9)	0
Photophobia	114 (47.1)	5 (2.1)	6 (2.4)	0
Eye irritation	103 (42.6)	12 (5.0)	13 (5.3)	0
Foreign body sensation in eyes	106 (43.8)	8 (3.3)	10 (4.1)	0
Eye pain	77 (31.8)	2 (0.8)	8 (3.3)	1 (0.4)
Cataract	49 (20.2)	17 (7.0)	25 (10.2)	6 (2.4)
Visual impairment	26 (10.7)	13 (5.4)	4 (1.6)	1 (0.4)
General disorders and administration site conditions				
Fatigue	47 (19.4)	9 (3.7)	48 (19.5)	6 (2.4)
Pyrexia	45 (18.6)	1 (0.4)	25 (10.2)	3 (1.2)
Oedema peripheral	26 (10.7)	1 (0.4)	22 (8.9)	0
Investigations				
Platelet count decreased	51 (21.1)	44 (18.2)	40 (16.3)	26 (10.6)
ALT increased	47 (19.4)	14 (5.8)	29 (11.8)	3 (1.2)
AST increased	37 (15.3)	3 (1.2)	13 (5.3)	0
GGT increased	36 (14.9)	22 (9.1)	11 (4.5)	4 (1.6)
Blood LDH increased	28 (11.6)	0	8 (3.3)	0
Metabolism and nutrition disorders				
Hypokalaemia	27 (11.2)	6 (2.5)	26 (10.6)	10 (4.1)
Hyperglycaemia	14 (5.8)	3 (1.2)	29 (11.8)	6 (2.4)
Musculoskeletal and connective tissue disorders				
Back pain	22 (9.1)	3 (1.2)	36 (14.6)	5 (2.0)
Arthralgia	21 (8.7)	0	25 (10.2)	2 (0.8)
Pain in extremity	14 (5.8)	0	25 (10.2)	2 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	29 (12.0)	0	33 (13.4)	0
Psychiatric disorders				
Insomnia	38 (15.7)	3 (1.2)	47 (19.1)	2 (0.8)
Injury, poisoning and procedural complications				
Infusion related reaction	8 (3.3)	1 (0.4)	42 (17.1)	4 (1.6)
Vascular disorders				
Hypertension	28 (11.6)	13 (5.4)	19 (7.7)	6 (2.4)

Serious adverse events occurred in 121 of 242 subjects (50.0%) in the belantamab mafodotin/Bd group and 90 of 246 subjects (36.6%) in the DAR/Bd group. Serious adverse events occurring in ≥2% of subjects were pneumonia (27 subjects, 11.2%), pyrexia (12 subjects, 5.0%), COVID-19 (11 subjects, 4.5%), COVID-19 pneumonia (8 subjects, 3.3%), and thrombocytopenia (8 subjects, 3.3%) in the belantamab mafodotin/Bd group; pneumonia (10 subjects, 4.1%), COVID-19 (10 subjects, 4.1%), pyrexia (9 subjects, 3.7%), and COVID-19 pneumonia (8 subjects, 3.3%) in the DAR/Bd group. A causal relationship to the study drug could not be ruled out for pneumonia (9 subjects), thrombocytopenia (8 subjects), pyrexia (3 subjects), COVID-19 (1 subject), and COVID-19 pneumonia (1 subject) in the belantamab mafodotin/Bd group; pneumonia (4 subjects), COVID-19 (3 subjects), and pyrexia (2 subjects) in the DAR/Bd group.

Adverse events led to treatment discontinuation of the study drug in 75 of 242 subjects (31.0%) in the belantamab mafodotin/Bd group and 46 of 246 subjects (18.7%) in the DAR/Bd group. Adverse events

leading to treatment discontinuation that occurred in ≥2% of subjects were peripheral sensory neuropathy (13 subjects, 5.4%), pneumonia (9 subjects, 3.7%), polyneuropathy (7 subjects, 2.9%), neuropathy peripheral (6 subjects, 2.5%), thrombocytopenia (5 subjects, 2.1%), and vision blurred (5 subjects, 2.1%) in the belantamab mafodotin/Bd group; neuropathy peripheral (11 subjects, 4.5%), peripheral sensory neuropathy (6 subjects, 2.4%), polyneuropathy (5 subjects, 2.0%), and COVID-19 pneumonia (5 subjects, 2.0%) in the DAR/Bd group. A causal relationship to the study drug could not be ruled out for peripheral sensory neuropathy (12 subjects), polyneuropathy (7 subjects), neuropathy peripheral (6 subjects), pneumonia (5 subjects), thrombocytopenia (5 subjects), and vision blurred (5 subjects) in the belantamab mafodotin/Bd group; neuropathy peripheral (11 subjects), peripheral sensory neuropathy (6 subjects), polyneuropathy (5 subjects), and COVID-19 pneumonia (3 subjects) in the DAR/Bd group.

7.3.2.2 Japan expansion cohort

Any adverse events as well as adverse events for which a causal relationship to the study drug could not be ruled out occurred in 10 of 10 subjects (100%) in the belantamab mafodotin/Bd group and 14 of 14 subjects (100%) in the DAR/Bd group. Adverse events occurring in ≥4 subjects in each group were thrombocytopenia, foreign body sensation in eyes, and vision blurred (7 subjects [70.0%] each); diarrhoea (6 subjects, 60.0%); nausea, decreased appetite, eye pain, photophobia, and malaise (4 subjects [40.0%] each) in the belantamab mafodotin/Bd group; thrombocytopenia (7 subjects, 50.0%); platelet count decreased, and insomnia (5 subjects [35.7%] each), diarrhoea, pyrexia, white blood cell count decreased, neuropathy peripheral, fall, and arthralgia (4 subjects [28.6%] each) in the DAR/Bd group.

Serious adverse events occurred in 7 of 10 subjects (70.0%) in the belantamab mafodotin/Bd group and 2 of 14 subjects (14.3%) in the DAR/Bd group. Serious adverse events occurring in ≥2 subjects in each group were COVID-19 (2 subjects, 20.0%) in the belantamab mafodotin/Bd group, for which a causal relationship to the study drug was ruled out. No serious adverse events occurred in ≥2 subjects in the DAR/Bd group.

Adverse events led to treatment discontinuation of the study drug in 1 of 10 subjects (10.0%) in the belantamab mafodotin/Bd group and no subjects in the DAR/Bd group. No adverse events led to treatment discontinuation of the study drug in ≥2 subjects in either group.

7.3.3 Global phase III study (DREAMM-8 study)

7.3.3.1 Main cohort

Adverse events occurred in 149 of 150 subjects (99.3%) in the belantamab mafodotin/Pd group and 139 of 145 subjects (95.9%) in the VPd group. A causal relationship to the study drug could not be ruled out for 143 of 150 subjects (95.3%) in the belantamab mafodotin/Pd group and 118 of 145 subjects (81.4%) in the VPd group. Table 84 shows adverse events occurring in ≥10% of subjects in either group.

Table 84. Adverse events occurring in ≥10% of subjects in either group

SOC PT (MedDRA/J ver.26.1)	Number of subjects (%)			
	Belantamab mafodotin/Pd N = 150		VPd N = 145	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	149 (99.3)	141 (94.0)	139 (95.9)	110 (75.9)
Infections and infestations				
COVID-19	56 (37.3)	10 (6.7)	31 (21.4)	3 (2.1)
Upper respiratory tract infection	40 (26.7)	2 (1.3)	25 (17.2)	0
Pneumonia	36 (24.0)	26 (17.3)	17 (11.7)	11 (7.6)
Urinary tract infection	23 (15.3)	6 (4.0)	13 (9.0)	1 (0.7)
COVID-19 pneumonia	18 (12.0)	16 (10.7)	6 (4.1)	6 (4.1)
Eye disorders				
Vision blurred	119 (79.3)	26 (17.3)	22 (15.2)	0
Dry eye	91 (60.7)	12 (8.0)	14 (9.7)	0
Foreign body sensation in eyes	91 (60.7)	9 (6.0)	9 (6.2)	0
Eye irritation	75 (50.0)	6 (4.0)	13 (9.0)	0
Photophobia	66 (44.0)	5 (3.3)	6 (4.1)	0
Eye pain	49 (32.7)	3 (2.0)	7 (4.8)	0
Cataract	40 (26.7)	9 (6.0)	15 (10.3)	6 (4.1)
Visual acuity reduced	34 (22.7)	20 (13.3)	8 (5.5)	1 (0.7)
Punctate keratitis	34 (22.7)	9 (6.0)	1 (0.7)	1 (0.7)
Corneal epithelial microcysts	34 (22.7)	12 (8.0)	0	0
Visual impairment	23 (15.3)	15 (10.0)	2 (1.4)	1 (0.7)
Blood and lymphatic system disorders				
Neutropenia	72 (48.0)	63 (42.0)	50 (34.5)	41 (28.3)
Thrombocytopenia	54 (36.0)	36 (24.0)	44 (30.3)	29 (20.0)
Anaemia	35 (23.3)	15 (10.0)	38 (26.2)	19 (13.1)
General disorders and administration site conditions				
Fatigue	40 (26.7)	9 (6.0)	32 (22.1)	7 (4.8)
Oedema peripheral	16 (10.7)	1 (0.7)	23 (15.9)	3 (2.1)
Pyrexia	29 (19.3)	1 (0.7)	10 (6.9)	2 (1.4)
Asthenia	15 (10.0)	3 (2.0)	20 (13.8)	7 (4.8)
Gastrointestinal disorders				
Diarrhoea	35 (23.3)	2 (1.3)	33 (22.8)	10 (6.9)
Constipation	23 (15.3)	2 (1.3)	33 (22.8)	2 (1.4)
Nausea	18 (12.0)	1 (0.7)	16 (11.0)	0
Investigations				
Platelet count decreased	30 (20.0)	22 (14.7)	22 (15.2)	18 (12.4)
Neutrophil count decreased	31 (20.7)	31 (20.7)	19 (13.1)	18 (12.4)
ALT increased	23 (15.3)	2 (1.3)	13 (9.0)	5 (3.4)
AST increased	15 (10.0)	4 (2.7)	11 (7.6)	3 (2.1)
Nervous system disorders				
Neuropathy peripheral	11 (7.3)	1 (0.7)	34 (23.4)	4 (2.8)
Dizziness	9 (6.0)	1 (0.7)	17 (11.7)	2 (1.4)
Peripheral sensory neuropathy	5 (3.3)	0	15 (10.3)	1 (0.7)
Musculoskeletal and connective tissue disorders				
Back pain	16 (10.7)	1 (0.7)	22 (15.2)	2 (1.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	26 (17.3)	2 (1.3)	11 (7.6)	1 (0.7)
Cough	20 (13.3)	1 (0.7)	11 (7.6)	0
Psychiatric disorders]				
Insomnia	20 (13.3)	2 (1.3)	18 (12.4)	1 (0.7)

Serious adverse events occurred in 95 of 150 subjects (63.3%) in the belantamab mafodotin/Pd group and 65 of 145 subjects (44.8%) in the VPd group. Serious adverse events occurring in ≥2% of subjects were pneumonia (27 subjects, 18.0%); COVID-19 pneumonia (17 subjects, 11.3%); COVID-19 (10 subjects, 6.7%); neutropenia (9 subjects, 6.0%); febrile neutropenia, and urinary tract infection (5 subjects [3.3%] each); acute kidney injury, pulmonary embolism, pneumocystis jirovecii pneumonia,

and respiratory tract infection (3 subjects [2.0%] each) in the belantamab mafodotin/Pd group; and pneumonia (11 subjects, 7.6%); COVID-19 pneumonia (6 subjects, 4.1%); thrombocytopenia (5 subjects, 3.4%); COVID-19, neutropenia, acute kidney injury, and pulmonary embolism (4 subjects [2.8%] each); febrile neutropenia, atrial fibrillation, cardiac failure, death, and sepsis (3 subjects [2.1%] each) in the VPd group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia (17 subjects); neutropenia (8 subjects); febrile neutropenia (4 subjects); pneumocystis jirovecii pneumonia (3 subjects); and pulmonary embolism (1 subject) in the belantamab mafodotin/Pd group; pneumonia and neutropenia (4 subjects each); febrile neutropenia and thrombocytopenia (3 subjects each), COVID-19 pneumonia, acute kidney injury, and pulmonary embolism (1 subject each) in the VPd group.

Adverse events led to treatment discontinuation of the study drug in 22 of 150 subjects (14.7%) in the belantamab mafodotin/Pd group, and 18 of 145 subjects (12.4%) in the VPd group. There were no adverse events leading to treatment discontinuation of the study drug that occurred in ≥2% of subjects.

7.3.3.2 Japan expansion cohort

Adverse events occurred in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 6 of 7 subjects (85.7%) in the belantamab mafodotin/Pd group and 5 of 5 subjects (100%) in the VPd group. Adverse events occurring in ≥40% of subjects in each group were ALT increased (5 subjects, 71.4%); vision blurred (6 subjects, 85.7%); diarrhoea (4 subjects, 57.1%); constipation, AST increased, foreign body sensation in eyes, and hypogammaglobulinaemia (3 subjects [42.9%] each) in the belantamab mafodotin/Pd group; and constipation, thrombocytopenia, leukopenia, and injection site reaction (2 subjects [40.0%] each) in the VPd group.

Serious adverse events occurred in 3 of 7 subjects (42.9%) in the belantamab mafodotin/Pd group and no serious adverse events occurred in the VPd group. No serious adverse events occurred in ≥2 subjects.

Adverse events led to treatment discontinuation of the study drug in 1 of 7 subjects (14.3%) in the belantamab mafodotin/Pd group and 1 of 5 subjects (20.0%) in the VPd group. No adverse events led to treatment discontinuation of the study drug in ≥2 subjects.

7.3.4 Global phase III study (DREAMM-3 study)

Adverse events occurred in 212 of 217 subjects (97.7%) in the belantamab mafodotin monotherapy group and 97 of 102 subjects (95.1%) in the Pd group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 187 of 217 subjects (86.2%) in the belantamab mafodotin monotherapy group and 79 of 102 subjects (77.5%) in the Pd group. Table 85 shows adverse events occurring in ≥10% of subjects in either group.

Table 85. Adverse events occurring in ≥10% of subjects in either group

SOC PT (MedDRA/J ver.26.1)	Number of subjects (%)			
	Belantamab mafodotin monotherapy N = 217		Pd N = 102	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	212 (97.7)	174 (80.2)	97 (95.1)	80 (78.4)
Blood and lymphatic system disorders				
Thrombocytopenia	76 (35.0)	53 (24.4)	34 (33.3)	17 (16.7)
Anaemia	62 (28.6)	37 (17.1)	34 (33.3)	20 (19.6)
Neutropenia	27 (12.4)	20 (9.2)	41 (40.2)	36 (35.3)
Eye disorders				
Vision blurred	105 (48.4)	13 (6.0)	5 (4.9)	0
Foreign body sensation in eyes	80 (36.9)	3 (1.4)	5 (4.9)	0
Dry eye	81 (37.3)	9 (4.1)	3 (2.9)	0
Photophobia	63 (29.0)	3 (1.4)	4 (3.9)	0
Eye irritation	63 (29.0)	2 (0.9)	3 (2.9)	0
Eye pain	48 (22.1)	1 (0.5)	0	0
Visual acuity reduced	40 (18.4)	16 (7.4)	1 (1.0)	0
Keratopathy	23 (10.6)	8 (3.7)	1 (1.0)	0
Punctate keratitis	23 (10.6)	8 (3.7)	0	0
Investigations				
Platelet count decreased	34 (15.7)	21 (9.7)	13 (12.7)	7 (6.9)
AST increased	35 (16.1)	4 (1.8)	6 (5.9)	0
Blood LDH increased	35 (16.1)	0	1 (1.0)	0
GGT increased	30 (13.8)	10 (4.6)	6 (5.9)	3 (2.9)
Neutrophil count decreased	20 (9.2)	12 (5.5)	16 (15.7)	13 (12.7)
White blood cell count decreased	14 (6.5)	3 (1.4)	11 (10.8)	6 (5.9)
Infections and infestations				
COVID-19	37 (17.1)	5 (2.3)	16 (15.7)	4 (3.9)
Pneumonia	12 (5.5)	5 (2.3)	11 (10.8)	9 (8.8)
General disorders and administration site conditions				
Pyrexia	45 (20.7)	3 (1.4)	11 (10.8)	0
Fatigue	22 (10.1)	2 (0.9)	15 (14.7)	3 (2.9)
Oedema peripheral	6 (2.8)	0	11 (10.8)	0
Gastrointestinal disorders				
Diarrhoea	29 (13.4)	3 (1.4)	12 (11.8)	2 (2.0)
Nausea	25 (11.5)	0	5 (4.9)	0

Serious adverse events occurred in 99 of 217 subjects (45.6%) in the belantamab mafodotin monotherapy group and 44 of 102 subjects (43.1%) in the Pd group. Serious adverse events occurring in ≥2 subjects in each group were thrombocytopenia (9 subjects, 4.1%); pyrexia (8 subjects, 3.7%); pneumonia (7 subjects, 3.2%); anaemia (6 subjects, 2.8%); COVID-19 (5 subjects, 2.3%); infusion related reaction and platelet count decreased (4 subjects [1.8%] each); COVID-19 pneumonia, septic shock, subdural haematoma, atrial fibrillation, fall, femur fracture, pathological fracture, spinal cord compression, and urinary tract infection (3 subjects [1.4%] each); sepsis, cardiac failure, acute kidney injury, bone pain, cerebral haemorrhage, encephalopathy, gastrointestinal haemorrhage, haematuria, hypercalcaemia, lower respiratory tract infection, osteomyelitis, plasma cell myeloma, pneumonitis, and vomiting (2 subjects [0.9%] each) in the belantamab mafodotin monotherapy group; and pneumonia (9 subjects, 8.8%), COVID-19 pneumonia, febrile neutropenia (5 subjects [4.9%] each), COVID-19 (4 subjects, 3.9%), sepsis (3 subjects, 2.9%), respiratory tract infection (2 subjects, 2.0%) in the Pd group. Among these events, a causal relationship to the study drug could not be ruled out for thrombocytopenia (6 subjects); infusion related reaction and platelet count decreased (4 subjects each); anaemia (2 subjects); pneumonia, pyrexia, atrial fibrillation, urinary tract infection, cerebral haemorrhage,

pneumonitis, and vomiting (1 subject each) in the belantamab mafodotin monotherapy group; and pneumonia (5 subjects); febrile neutropenia (4 subjects); sepsis (2 subjects) in the Pd group.

Adverse events led to treatment discontinuation of the study drug in 35 of 217 subjects (16.1%) in the belantamab mafodotin monotherapy group and 19 of 102 subjects (18.6%) in the Pd group. Adverse events leading to treatment discontinuation of the study drug that occurred in ≥2 subjects in each group were thrombocytopenia (5 subjects, 2.3%); vision blurred (3 subjects, 1.4%); septic shock, hypercalcaemia, and spinal cord compression (2 subjects [0.9%] each) in the belantamab mafodotin monotherapy group; and COVID-19 and sepsis (2 subjects [2.0%] each) in the Pd group. Among these events, a causal relationship to the study drug could not be ruled out for vision blurred (3 subjects) and thrombocytopenia (1 subject) in the belantamab mafodotin monotherapy group and sepsis (1 subject) in the Pd group.

7.3.5 Foreign phase I study (DREAMM-1 study)

7.3.5.1 Part 1

Adverse events occurred in 37 of 38 subjects (97.4%) and adverse events for which a causal relationship to belantamab mafodotin could not be ruled out occurred in 34 of 38 subjects (89.5%). Adverse events occurring in ≥10% of subjects were nausea (18 subjects, 47.4%); fatigue (17 subjects, 44.7%); thrombocytopenia (14 subjects, 36.8%); vision blurred and anaemia (12 subjects [31.6%] each); chills and AST increased (9 subjects [23.7%] each); pyrexia and dry eye (8 subjects [21.1%] each); neutropenia and cough (7 subjects [18.4%] each); arthralgia, hypercalcaemia, upper respiratory tract infection, epistaxis, and headache (6 subjects [15.8%] each); diarrhoea, vomiting, back pain, pain in extremity, blood creatine phosphokinase increased, blood LDH increased, and hyponatraemia (5 subjects [13.2%] each); photophobia, visual impairment, musculoskeletal chest pain, myalgia, platelet count decreased, and decreased appetite (4 subjects [10.5%] each).

Serious adverse events occurred in 13 of 38 subjects (34.2%). Serious adverse events that occurred in ≥2 subjects were pneumonia and pyrexia (2 subjects [5.3%] each). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for pneumonia and pyrexia in 1 subject each.

Adverse events led to treatment discontinuation of belantamab mafodotin in 4 of 38 subjects (10.5%). No adverse events led to treatment discontinuation of belantamab mafodotin in ≥2 subjects.

7.3.5.2 Part 2 (MM cohort)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to belantamab mafodotin could not be ruled out occurred in 34 of 35 subjects (97.1%). Adverse events occurring in ≥20% of subjects were vision blurred (18 subjects, 51.4%); cough (14 subjects, 40.0%); AST increased, platelet count decreased, and dry eye (13 subjects [37.1%] each); nausea (11 subjects, 31.4%); photophobia, diarrhoea, pyrexia, and anaemia (10 subjects [28.6%] each); upper respiratory tract

infection, chills, and thrombocytopenia (9 subjects [25.7%] each); pneumonia and fatigue (8 subjects [22.9%] each); ALT increased, γ-glutamyl transpeptidase (GGT) increased, constipation, and back pain (7 subjects [20.0%] each).

Serious adverse events occurred in 17 of 35 subjects (48.6%). Reported serious adverse events were pneumonia (5 subjects, 14.3%); infusion related reaction (2 subjects, 5.7%); adenovirus infection, appendicitis, arthralgia, atrial fibrillation, back pain, bacteraemia, cholecystitis infective, encephalopathy, fall, febrile neutropenia, gastroenteritis salmonella, haematuria, haemorrhage intracranial, influenza, lower respiratory tract infection, pericardial effusion, pneumonia haemophilus, pyrexia, respiratory tract infection, retinal detachment, and salmonellosis (1 subject [2.9%] each). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for pneumonia and infusion related reaction (2 subjects each); gastroenteritis salmonella, haemorrhage intracranial, lower respiratory tract infection, pericardial effusion, pyrexia, respiratory tract infection, and salmonellosis (1 subject each).

Adverse events led to treatment discontinuation of belantamab mafodotin in 4 of 35 subjects (11.4%). Reported adverse events leading to treatment discontinuation of belantamab mafodotin were ALT increased, AST increased, blood creatine phosphokinase increased, cough, fatigue, keratopathy, and thrombocytopenia (1 subject [2.9%] each). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for ALT increased, AST increased, blood creatine phosphokinase increased, thrombocytopenia (1 subject each).

7.3.6 Foreign phase I/II study (DREAMM-6 study) (Arm B, belantamab mafodotin/Bd)

Adverse events[95)] occurred in all subjects. Adverse events that were determined to have a causal relationship to the study drug occurred in 12 of 12 subjects (100%) in the 1.9 mg/kg Q6W (Stretch) group; 12 of 12 subjects (100%) in the 1.9 mg/kg Q3W (Single) group; 12 of 12 subjects (100%) in the 2.5 mg/kg Q6W (step-down Stretch) group; 12 of 12 subjects (100%) in the 2.5 mg/kg Q6W (Stretch) group; 12 of 13 subjects (92.3%) in the 2.5 mg/kg Q3W (Split) group; 18 of 18 subjects (100%) in the 2.5 mg/kg Q3W (Single) group; 12 of 12 subjects (100%) in the 3.4 mg/kg Q3W (Split) group; 16 of 16 subjects (100%) in the 3.4 mg/kg Q3W (Single) group. Adverse events occurring in ≥30% of subjects in each group were as follows. In the 1.9 mg/kg Q6W (Stretch) group, keratopathy (9 subjects, 75.0%); diarrhoea and platelet count decreased (6 subjects [50.0%] each); visual acuity reduced, nausea, and thrombocytopenia (4 subjects [33.3%] each). In the 1.9 mg/kg Q3W (Single) group, keratopathy (11 subjects, 91.7%); platelet count decreased (9 subjects, 75.0%); constipation (8 subjects, 66.7%); visual acuity reduced and insomnia (6 subjects [50.0%] each); diarrhoea, fatigue, and thrombocytopenia (5 subjects [41.7%] each); peripheral sensory neuropathy and dyspnoea (4 subjects [33.3%] each). In the 2.5 mg/kg Q6W (step-down Stretch) group, keratopathy (12 subjects, 100%); platelet count decreased (7 subjects, 58.3%); diarrhoea (6 subjects, 50.0%); vision blurred, constipation, nausea, AST increased,

95) See Section 7.1.3.2 for details of the regimen in each treatment group.

and lymphocyte count decreased (5 subjects [41.7%] each); visual acuity reduced, COVID-19, fatigue, and oedema peripheral (4 subjects [33.3%] each). In the 2.5 mg/kg Q6W (Stretch) group, keratopathy (12 subjects, 100%); platelet count decreased (7 subjects, 58.3%); GGT increased (6 subjects, 50.0%); vision blurred, fatigue, oedema peripheral, and thrombocytopenia (5 subjects [41.7%] each); visual acuity reduced, AST increased, headache, and insomnia (4 subjects [33.3%] each). In the 2.5 mg/kg Q3W (Split) group, keratopathy and thrombocytopenia (10 subjects [76.9%] each); vision blurred (5 subjects, 38.5%); photophobia, upper respiratory tract infection, diarrhoea, fatigue, arthralgia, bone pain, and cough (4 subjects [30.8%] each). In the 2.5 mg/kg Q3W (Single) group, keratopathy (15 subjects, 83.3%); vision blurred (12 subjects, 66.7%), platelet count decreased (10 subjects, 55.6%); upper respiratory tract infection (9 subjects, 50.0%); diarrhoea and nausea (8 subjects [44.4%] each); constipation, photophobia, fatigue, neuropathy peripheral, thrombocytopenia, and insomnia (6 subjects [33.3%] each). In the 3.4 mg/kg Q3W (Split) group, keratopathy (10 subjects, 83.3%), thrombocytopenia (9 subjects, 75.0%) and fatigue (5 subjects, 41.7%). In the 3.4 mg/kg Q3W (Single) group, keratopathy (15 subjects, 93.8%); thrombocytopenia (9 subjects, 56.3%); neuropathy peripheral (8 subjects, 50.0%); vision blurred, constipation, and nausea (7 subjects [43.8%] each); upper respiratory tract infection (6 subjects, 37.5%); vomiting, platelet count decreased, and oedema peripheral (5 subjects [31.3%] each).

Serious adverse events occurred in 8 of 12 subjects (66.7%) in the 1.9 mg/kg Q6W (Stretch) group; 8 of 12 subjects (66.7%) in the 1.9 mg/kg Q3W (Single) group; 6 of 12 subjects (50.0%) in the 2.5 mg/kg Q6W (step-down Stretch) group; 6 of 12 subjects (50.0%) in the 2.5 mg/kg Q6W (Stretch) group; 7 of 13 subjects (53.8%) in the 2.5 mg/kg Q3W (Split) group; 13 of 18 subjects (72.2%) in the 2.5 mg/kg Q3W (Single) group; 6 of 12 subjects (50.0%) in the 3.4 mg/kg Q3W (Split) group; 9 of 16 subjects (56.3%) in the 3.4 mg/kg Q3W (Single) group. Serious adverse events occurring in ≥2 subjects in each group were as follows: pneumonia (3 subjects, 25.0%), diarrhoea (2 subjects, 16.7%) in the 1.9 mg/kg Q6W (Stretch) group; lower respiratory tract infection (2 subjects, 16.7%) in the 1.9 mg/kg Q3W (Single) group; femur fracture (2 subjects, 16.7%) in the 2.5 mg/kg Q6W (Stretch) group; influenza and upper respiratory tract infection (2 subjects [15.4%] each) in the 2.5 mg/kg Q3W (Split) group; pneumonia, lower respiratory tract infection, fall (2 subjects [11.1%] each) in the 2.5 mg/kg Q3W (Single) group; staphylococcal bacteraemia (2 subjects, 16.7%) in the 3.4 mg/kg Q3W (Split) group. No serious adverse events occurring in ≥2 subjects were reported in the 2.5 mg/kg Q6W (step-down Stretch) group or 3.4 mg/kg Q3W (Single) group. A causal relationship to the study drug could not be ruled out for pneumonia and diarrhoea (1 subject [8.3%] each) in the 1.9 mg/kg Q6W (Stretch) group, femur fracture (1 subject, 8.3%) in the 2.5 mg/kg Q6W (Stretch) group, and pneumonia (1 subject, 5.6%) in the 2.5 mg/kg Q3W (Single) group.

Adverse events leading to treatment discontinuation of the study drug occurred in 3 of 12 subjects (25.0%) in the 1.9 mg/kg Q6W (Stretch) group; 1 of 12 subjects (8.3%) in the 1.9 mg/kg Q3W (Single) group; 5 of 12 subjects (41.7%) in the 2.5 mg/kg Q6W (step-down Stretch) group; 4 of 12 subjects (33.3%) in the 2.5 mg/kg Q6W (Stretch) group; 4 of 13 subjects (30.8%) in the 2.5 mg/kg Q3W (Split)

group; 7 of 18 subjects (38.9%) in the 2.5 mg/kg Q3W (Single) group; 7 of 12 subjects (58.3%) in the 3.4 mg/kg Q3W (Split) group; 7 of 16 subjects (43.8%) in the 3.4 mg/kg Q3W (Single) group. Adverse events leading to treatment discontinuation of the study drug that occurred in ≥2 subjects in each group were neuropathy peripheral (2 subjects, 15.4%) in the 2.5 mg/kg Q3W (Split) group; insomnia and neuralgia (2 subjects [11.1%] each) in the 2.5 mg/kg Q3W (Single) group; neuropathy peripheral (2 subjects, 16.7%) in the 3.4 mg/kg Q3W (Split) group; neuropathy peripheral (3 subjects, 18.8%) in the 3.4 mg/kg Q3W (Single) group. A causal relationship to the study drug could not be ruled out for any of these events. No adverse events led to treatment discontinuation of the study drug in ≥2 subjects in the remaining groups.

7.3.7 Foreign phase II study (DREAMM-2 study)

Adverse events occurred in 93 of 95 subjects (97.9%) in the 2.5 mg/kg (frozen liquid) group, 99 of 99 subjects (100%) in the 3.4 mg/kg (frozen liquid) group, and 24 of 24 subjects (100%) in the 3.4 mg/kg (lyophilized powder) group. Among these events, a causal relationship to belantamab mafodotin could not be ruled out in 84 of 95 subjects (88.4%) in the 2.5 mg/kg (frozen liquid) group; 94 of 99 subjects (94.9%) in the 3.4 mg/kg (frozen liquid) group, and 24 of 24 subjects (100%) in the 3.4 mg/kg (lyophilized powder) group. Adverse events occurring in ≥20% of subjects in each formulation group were as follows. In the 2.5 mg/kg (frozen liquid) group, keratopathy (67 subjects, 70.5%); anaemia (26 subjects, 27.4%); nausea (24 subjects, 25.3%); thrombocytopenia (23 subjects, 24.2%); vision blurred and pyrexia (22 subjects [23.2%] each); AST increased (21 subjects, 22.1%); and arthralgia (19 subjects, 20.0%). In the 3.4 mg/kg (frozen liquid) group, keratopathy (74 subjects, 74.7%); thrombocytopenia (46 subjects, 46.5%); nausea (32 subjects, 32.3%); vision blurred (30 subjects, 30.3%); anaemia (38 subjects, 38.4%); fatigue (28 subjects, 28.3%); AST increased (24 subjects, 24.2%); vomiting and upper respiratory tract infection (22 subjects [22.2%] each); and cough (20 subjects, 20.2%). In the 3.4 mg/kg (lyophilized powder) group, keratopathy (23 subjects, 95.8%); fatigue (12 subjects, 50.0%); vision blurred, thrombocytopenia, and anaemia (8 subjects [33.3%] each); AST increased and back pain (6 subjects [25.0%] each); dry eye, intraocular pressure increased, decreased appetite, hyponatraemia, and headache (5 subjects [20.8%] each).

Serious adverse events occurred in 43 of 95 subjects (45.3%) in the 2.5 mg/kg (frozen liquid) group, 53 of 99 subjects (53.5%) in the 3.4 mg/kg (frozen liquid) group, and 15 of 24 subjects (62.5%) in the 3.4 mg/kg (lyophilized powder) group. Serious adverse events occurring in ≥2 subjects in each formulation group were as follows. In the 2.5 mg/kg (frozen liquid) group, pneumonia and pyrexia (7 subjects [7.4%] each); hypercalcaemia (4 subjects, 4.2%); infusion related reaction (3 subjects, 3.2%); sepsis, gastrointestinal haemorrhage, acute kidney injury, pleural effusion, hypokalaemia, staphylococcal sepsis, and vascular device infection (2 subjects [2.1%] each). In the 3.4 mg/kg (frozen liquid) group, pneumonia (14 subjects, 14.1%); pyrexia (5 subjects, 5.1%); anaemia, cerebral haemorrhage, febrile neutropenia, and thrombocytopenia (3 subjects [3.0%] each); cellulitis, epistaxis, escherichia urinary tract infection, gastrointestinal haemorrhage, general physical health deterioration, hyperviscosity syndrome, influenza, infusion related reaction, osteolysis, sepsis, and upper respiratory

tract infection (2 subjects [2.0%] each). In the 3.4 mg/kg (lyophilized powder) group, thrombocytopenia (3 subjects, 12.5%) and dehydration (2 subjects, 8.3%). Among these events, a causal relationship to belantamab mafodotin could not be ruled out for the following events: infusion related reaction (3 subjects); pneumonia, pyrexia, and sepsis (2 subjects each); acute kidney injury and hypokalaemia (1 subject each) in the 2.5 mg/kg (frozen liquid) group; pneumonia (5 subjects); pyrexia (4 subjects); thrombocytopenia (3 subjects); infusion related reaction and sepsis (2 subjects each); cerebral haemorrhage, febrile neutropenia, cellulitis, epistaxis, escherichia urinary tract infection, influenza, and upper respiratory tract infection (1 subject each) in the 3.4 mg/kg (frozen liquid) group; and thrombocytopenia (2 subjects) in the 3.4 mg/kg (lyophilized powder) group.

Adverse events led to treatment discontinuation of belantamab mafodotin in 11 of 95 subjects (11.6%) in the 2.5 mg/kg (frozen liquid) group, 12 of 99 subjects (12.1%) in the 3.4 mg/kg (frozen liquid) group, and 2 of 24 subjects (8.3%) in the 3.4 mg/kg (lyophilized powder) group. Adverse events leading to treatment discontinuation of belantamab mafodotin that occurred in ≥2 subjects in each formulation group were keratopathy (3 subjects, 3.2%) in the 2.5 mg/kg (frozen liquid) group, and cerebral haemorrhage (3 subjects, 3.0%), keratopathy (3 subjects, 3.0%), and pneumonia (2 subjects, 2.0%) in the 3.4 mg/kg (frozen liquid) group, and no events in the 3.4 mg/kg (lyophilized powder) group. Among these events, a causal relationship to belantamab mafodotin could not be ruled out for keratopathy (3 subjects) in the 2.5 mg/kg (frozen liquid) group; and keratopathy (3 subjects) and cerebral haemorrhage (1 subject) in the 3.4 mg/kg (frozen liquid) group.

7.3.8 Foreign phase I study (DREAMM-12 study, Part 1)

Adverse events occurred in 10 of 10 subjects (100%) with normal/mild renal impairment, 8 of 9 subjects (88.9%) with severe renal impairment, and 4 of 4 subjects (100%) with other renal impairment status. Adverse events for which a causal relationship to belantamab mafodotin could not be ruled out occurred in 8 of 10 subjects (80.0%) with normal/mild renal impairment, 7 of 9 subjects (77.8%) with severe renal impairment, and 4 of 4 subjects (100%) with other renal impairment status. Adverse events occurring in ≥30% of subjects in each patient group were vision blurred, eye irritation, and foreign body sensation in eyes (5 subjects [50.0%] each); eye pain, anaemia, and dry eye (4 subjects [40.0%] each); and visual impairment (3 subjects, 30.0%) in the normal/mild renal impairment group; vision blurred (5 subjects, 55.6%); dry eye (4 subjects, 44.4%); eye irritation, photophobia, and thrombocytopenia (3 subjects [33.3%] each) in the severe renal impairment group; and vision blurred, dry eye, hypercalcaemia, acute kidney injury, and chills (2 subjects [50.0%] each) in the other renal impairment status group.

Serious adverse events occurred in 3 of 10 subjects (30.0%) in the normal/mild renal impairment group; 4 of 9 subjects (44.4%) in the severe renal impairment group; and 2 of 4 subjects (50.0%) in the other renal impairment status group. Serious adverse events occurring in ≥2 subjects in each patient group were chronic kidney disease (2 subjects, 22.2%) in the severe renal impairment group, and no events in

the other 2 groups. A causal relationship to belantamab mafodotin could not be ruled out for chronic kidney disease in 1 subject.

Adverse events leading to treatment discontinuation of belantamab mafodotin occurred in 1 of 10 subjects (10.0%) in the normal/mild renal impairment group, 1 of 9 subjects (11.1%) in the severe renal impairment group, and no events in the other renal impairment status group. No adverse events leading to treatment discontinuation of belantamab mafodotin occurred in ≥2 subjects in any patient group.

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

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

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

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

The new drug application data (CTD 5.3.5.1-4, CTD 5.3.5.1-5) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that belantamab mafodotin has efficacy in the treatment of relapsed or refractory MM, and that belantamab mafodotin has acceptable safety in view of its benefits. The drug product and its drug substance are both classified as powerful drugs. Belantamab mafodotin binds to BCMA expressed on the tumor cell membrane. Upon internalization into the cell, free cys-mcMMAF is released from the antibody component, which is thought to induce apoptosis and other effects, leading to inhibition of tumor growth. It is therefore clinically meaningful to make belantamab mafodotin, a drug with a new active ingredient, available as a new treatment option for relapsed or refractory MM. PMDA considers that the efficacy, safety, the dosage regimen, and post-marketing investigations for belantamab mafodotin should be further evaluated.

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

Review Report (2)

April 8, 2025

Product Submitted for Approval

Brand Name	Blenrep for I.V. Infusion 100 mg
Non-proprietary Name	Belantamab Mafodotin (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 13, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

In view of the discussions in Section "7.R.2 Efficacy" in Review Report (1), PMDA concluded that the results including the following demonstrate the efficacy of belantamab mafodotin/Bd and belantamab mafodotin/Pd in the treatment of patients with relapsed or refractory MM.

- DREAMM-7 study: The analysis of PFS determined by an independent review committee according to the IMWG criteria, the primary endpoint, demonstrated the superiority of belantamab mafodotin/Bd over DAR/Bd.
- DREAMM-8 study: The analysis of PFS determined by an independent review committee according to the IMWG criteria, the primary endpoint, demonstrated the superiority of belantamab mafodotin/Pd over VPd.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above, and the following comment was made by the expert advisor.

- The efficacy of belantamab mafodotin monotherapy has not been clarified; therefore, the results from the DREAMM-3 study, in which belantamab mafodotin monotherapy was evaluated, should be provided to healthcare professionals.

In light of the above discussions at the Expert Discussion, PMDA instructed the applicant to include the results from the DREAMM-3 study in the package insert to ensure that this information is provided to healthcare professionals in an appropriate manner. The applicant agreed with the instruction.

1.2 Safety

In view of the discussions in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that adverse events that require particular attention when belantamab mafodotin/Bd or belantamab mafodotin/Pd is used are eye disorders, cytopenia, infections, gastrointestinal disorders, bleeding, infusion reaction, ILD, and second primary malignancies.

Although the use of belantamab mafodotin requires particular caution due to the risk of the adverse events described above, PMDA concluded that treatment with belantamab mafodotin/Bd and belantamab mafodotin/Pd is tolerable provided that appropriate measures, such as monitoring and management of adverse events, are taken by a physician with sufficient knowledge and experience in hematopoietic malignancy treatment, in collaboration with an ophthalmologist.

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

1.3 Clinical positioning and indication

In view of the discussions in Section "7.R.4.1 Clinical positioning and indication" of Review Report (1), PMDA concluded that it is appropriate to include the following precautionary statements in the Precautions Concerning Indication section in the package insert and to specify the indication of belantamab mafodorin as "relapsed or refractory multiple myeloma."

Precautions Concerning Indication

- Eligible patients for belantamab mafodotin must have received at least 1 prior line of standard of care therapy, and MM is non-responsive to the therapy or relapsed after treatment.
- Whether a patient is eligible for treatment with belantamab mafodotin should be decided by physicians who are fully familiar with prior therapy and other details of patients enrolled in the clinical studies presented in the "Clinical Studies" section, and have a thorough understanding of the efficacy and safety of belantamab mafodotin.

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

1.4 Dosage and administration

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

Dosage and Administration

In combination with bortezomib and dexamethasone:

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg administered for the first dose as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition.

In combination with pomalidomide and dexamethasone:

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second dose, administered as an intravenous infusion over at least 30 minutes every 4 weeks. The dose should be reduced depending on the patient's condition.

Precautions Concerning Dosage and Administration

- The antineoplastic agent to be co-administered with belantamab mafodotin should be used by physicians who are fully familiar with the details in the "Clinical Studies" section.
- For patients receiving belantamab mafodotin in combination with bortezomib and dexamethasone, administration of belantamab mafodotin alone should be continued after the end of the combination therapy.
- If the patient develops an adverse drug reaction following administration of belantamab mafodotin, the dose of belantamab mafodotin must be interrupted, reduced, or treatment must be discontinued in accordance with the following guidelines.

Dose levels for reductions

	Belantamab mafodotin/Bd	Belantamab mafodotin/Pd
Usual dose	2.5 mg/kg every 3 weeks	2.5 mg/kg for the first dose. For the second and subsequent doses, 1.9 mg/kg every 4 weeks
Dose reduction by 1 level	1.9 mg/kg every 3 weeks	1.9 mg/kg every 8 weeks
Dose reduction by 2 levels	Not applicable	1.4 mg/kg every 8 weeks

Dose interruption, reduction, and treatment discontinuation guidelines for adverse drug reactions

Adverse drug reaction	Severity[Note 1)]	Action
Corneal examination findings and vision change[Note 2)]	Grade 1: Corneal examination findings Mild[Note 3)] superficial punctate keratopathy (documented worsening from baseline, with or without symptoms) Change in BCVA See Grade 1 in the table below.	Continue treatment.
	Grade 2: Corneal examination findings Moderate[Note 3)] superficial punctate keratopathy, patchy microcyst-like deposits, peripheral sub-epithelial haze, or a new peripheral stromal opacity Change in BCVA See Grade 2 in the table below.	Withhold treatment until both corneal examination findings and BCVA resolve to Grade ≤1. After resolution, resume treatment at a dose reduced by 1 level.[Note 4)]
	Grade 3: Corneal examination findings Severe[Note 3)] superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, central sub-epithelial haze, or a new central stromal opacity Change in BCVA See Grade 3 in the table below.	
	Grade 4: Corneal examination findings Corneal epithelium defect Change in BCVA See Grade 4 in the table below.	Discontinue treatment.
Platelet count decreased	Grade 3	Without bleeding: • At 2.5 mg/kg: reduce the dose to 1.9 mg/kg, and continue treatment.[Note 5)] • At ≤1.9 mg/kg: continue treatment at the same dose level.[Note 5)] With bleeding: • Withhold treatment until resolution to Grade ≤2. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Withhold treatment until resolution to Grade ≤3. Consider resuming treatment only if there is no bleeding after resolution: • At 2.5 mg/kg: resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: resume treatment at the pre-interruption dose level. • If platelet count decreased is considered to be related to multiple myeloma, without bleeding, and resolves with transfusion to 25,000/μL, treatment may be resumed at the pre-interruption dose level.

Infusion reaction	Grade 2	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume at a reduced infusion rate (no more than half the rate at which the symptoms initially appeared). Consider prophylactic medication when resuming infusion and for subsequent infusions.
	Grade 3	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume infusion at a rate 1/4 to 1/8 of the rate at which the symptoms initially appeared. Consider prophylactic medication when resuming infusion. For subsequent infusions, prophylactic medication should be administered.
	Grade 4	Discontinue treatment.
Other adverse drug reactions	Grade 3	Withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Consider treatment discontinuation. If treatment is to be continued, withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.

Note 1) With the exception of corneal examination findings and vision change, adverse drug reactions were graded according to CTCAE v. 5.0.
Note 2) Examination results may differ between the left and right eyes. The severity should be determined based on the most severe corneal findings or vision change in either eye.
Note 3) For the assessment of superficial punctate keratopathy, see the relevant materials provided by the marketing authorization holder.
Note 4) For combination therapy with POM and DEX: if an adverse drug reaction occurs before the second dose, 1.9 mg/kg should be administered every 4 weeks from the second dose onward.
Note 5) For combination therapy with BOR and DEX: if the decreased platelet count resolves to Grade ≤2, the original dose level may be used.

Severity of change in BCVA due to eye disorder

Baseline BCVA	Grade 1	Grade 2	Grade 3	Grade 4
1.5	1.2	0.8-1.0	0.1-0.7	<0.1
1.2	1.0	0.6-0.9	0.1-0.5	<0.1
1.0	0.8-0.9	0.5-0.7	0.1-0.4	<0.1
0.9	0.6-0.8	0.4-0.5	0.1-0.3	<0.1
0.8	0.6-0.7	0.4-0.5	0.1-0.3	<0.1
0.7	0.5-0.6	0.3-0.4	0.1-0.2	<0.1
0.6	0.5	0.3-0.4	0.1-0.2	<0.1
0.5	0.4	0.3	0.1-0.2	<0.1
0.4	0.3	0.2	0.1	<0.1
0.3	—	0.2	0.1	<0.1
0.2	—	0.1	—	<0.1

- Make sure to confirm results of ophthalmologic examinations (corneal examination findings and vision change) which are to be performed before each of the first through fourth doses of belantamab mafodotin, and on an as-needed basis thereafter, to assess the severity and determine the dose level, taking ocular symptoms into account. Because examination results may differ between the left and right eyes, the severity should be determined based on the most severe corneal findings or vision change in either eye. If any vision change is noted, its association with belantamab mafodotin should be clarified. If the dose of belantamab mafodotin is reduced due to corneal findings or vision change, the dose should not be re-escalated.

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

The applicant additionally provided the following explanation about the "corneal examination findings and vision change" in the dose modification guidelines for belantamab mafodotin after the Expert Discussion:
In the clinical studies, among patients who experienced recurrence of an eye disorder after resumption of belantamab mafodotin following the onset of "corneal examination findings and vision change" defined as Grade 4 events [see Section "7.R.5.2 Dose modification of belantamab mafodotin" in Review Report (1)], only a limited number of patients had their treatment with belantamab mafodotin discontinued (1 of 31 subjects and 2 of 8 subjects[96)] in the DREAMM-7 and DREAMM-8 studies, respectively). Given that relapsed or refractory MM is a difficult to cure, life-threatening disease that requires long-term treatment, it is preferable not to mandate automatic discontinuation of treatment. Instead, in accordance with clinical study protocols, discontinuing treatment should be considered while leaving room for continuation of therapy when appropriate.

PMDA's view:
As in the discussion in Section "7.R.5.2 Dose modification of belantamab mafodotin" in Review Report (1), in the DREAMM-7 and DREAMM-8 studies, 94% (29 of 31) and 100% (8 of 8), respectively, of patients who developed Grade 4 eye disorders and subsequently resumed treatment experienced recurrence of Grade ≥2 eye disorders. Based on this situation, it is appropriate to specify that if Grade 4 eye disorders occur, treatment must be discontinued. However, the applicant's approach as described above may be acceptable provided the decision to resume treatment with belantamab mafodotin is made based on the patient's condition, and that continuous ophthalmologic monitoring is performed after resuming treatment.

Taken together, PMDA concluded that it is acceptable to establish dosing criteria consistent with the clinical study protocols (in the table below, only the Grade 4 portion is excerpted, and Grade 1-3 are not shown here) provided detailed information from the clinical studies regarding the number of patients who resumed treatment and the subsequent course of ocular events (including the outcome) is appropriately communicated to prescribing physicians, etc. using educational materials. The expert advisors supported the PMDA's conclusion.

96) The eye disorders in the 3 patients who discontinued treatment of belantamab mafodotin, resolved later.

Adverse drug reaction	Severity	Action
Corneal examination findings and vision change	Grade 4: Corneal examination findings Corneal epithelium defect Change in BCVA See Grade 4 in the table below.	Consider treatment discontinuation. If treatment is to be continued,[Note)] withhold treatment until both corneal examination findings and change in BCVA resolve to Grade ≤1. • In combination with Bd: after resolution, treatment may be resumed at a dose reduced by 1 level. • In combination with Pd: after resolution, treatment may be resumed at a dose reduced by 2 levels. Treatment must be discontinued if the event does not resolve and symptoms worsen after adequate action has been taken.

Note: The necessity of continuing treatment must be determined carefully based on the patient's condition. If treatment is to be continued, proper ocular management must be implemented.

Regarding the description of "2.5 mg/kg administered for the first dose" in the dosage and administration for the combination regimen with Bd, although the dose level of belantamab mafodotin can be modified according to the dose modification guidelines, given that the usual dosage, including the starting dose level, is 2.5 mg/kg, specifying "first dose" is not necessary and it was concluded that the following description should be used:

In combination with bortezomib and dexamethasone:
The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg administered as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition.

PMDA instructed the applicant to establish the Dosage and Administration and Precautions Concerning Dosage and Administration sections as described above, and the applicant agreed with this instruction.

1.5 Risk management plan (draft) and post-marketing investigations

In view of the discussions presented in Section "7.R.6 Risk management plan (draft)" in Review Report (1), PMDA has concluded that the risk management plan (draft) for belantamab mafodotin should include the safety and efficacy specifications presented in Table 86.

Table 86. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Eye disorders • Cytopenia • Infections	• Gastrointestinal disorders • Bleeding • ILD • Second primary malignancies • Infusion reaction	None
Efficacy specification		
None		

In view of the discussions in Section "7.R.7 Post-marketing investigations" in Review Report (1), PMDA concluded that post-marketing surveillance should be conducted to investigate the risk of developing gastrointestinal disorders, bleeding, and infusion reaction following administration of

belantamab mafodotin to patients with relapsed or refractory MM in clinical use, and that the survey implementation plan should be as follows:

- Gastrointestinal disorders, bleeding, and infusion reaction should be included in the safety specification for the survey.
- The applicant is required to re-examine the planned sample size and the duration of the follow-up period for the survey, taking into account the incidence and timing of onset in the clinical studies of the events to be included in the safety specification, namely, gastrointestinal disorders, bleeding events, and infusion reaction.

In addition, given the risk of eye disorders associated with belantamab mafodotin observed in clinical studies, PMDA concluded that, to ensure patient safety, appropriate measures [see Section 7.R.6 in Review Report (1)] should be implemented. Specifically, belantamab mafodotin should be administered to patients only by a prescribing physician who has gained a thorough understanding of the risk of eye disorders, as well as the preventive and management measures specified in the package insert, in collaboration with an ophthalmologist at a medical institution equipped to provide adequate medical care.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion shown above, at the same time, the following comment was made by the expert advisor.

- The incidence of infusion reaction was limited when belantamab mafodotin was administered in combination with Bd or Pd in the DREAMM-7 and DREAMM-8 studies. This may be attributable to the effect of co-administered DEX. However, in clinical settings, the dose level of DEX is expected to be reduced in some cases depending on the patient's condition; therefore, it is important to ensure that data on the incidence of infusion reaction is collected in the post-marketing surveillance.

Based on the discussions at the Expert Discussion, PMDA instructed the applicant to re-examine the survey implementation plan, and the applicant responded as follows:

- The risk of gastrointestinal disorders, bleeding, and infusion reaction following administration of belantamab mafodotin in clinical settings will be selected as the objective of the survey.
- Gastrointestinal disorders, bleeding, and infusion reaction will be included in the safety specification for this survey.
- A planned sample size of 160 patients and a follow-up period of 1 year from the start of treatment with belantamab mafodotin will be selected, taking into account the incidence and timing of onset in the clinical studies of the events to be included in the safety specification, namely, gastrointestinal disorders, bleeding, and infusion reaction.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that under the risk management plan (draft) for belantamab mafodotin, the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 87 and Table 88.

Table 87. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate educational materials for healthcare professionals (primarily for prescribing physicians and ophthalmologists) (the contents of the materials include collaboration between prescribing medical institutions and ophthalmologists and ensuring prescription by physicians who have received the information) • Organize and disseminate educational materials for patients

Table 88. Outline of use-results survey (draft)

Objective	To investigate the risk of gastrointestinal disorders, bleeding, and infusion reaction following administration of belantamab mafodotin in clinical settings
Survey method	Continuous survey method
Population	Patients with relapsed or refractory MM treated with belantamab mafodotin
Observation period	Up to 1 year from the start of treatment with belantamab mafodotin
Planned sample size	160 patients (146 patients who are included in safety analyses)
Main survey items	Safety specification: gastrointestinal disorders, bleeding, and infusion reaction Other main survey items: baseline demographics and disease characteristics of patients (e.g., age, sex, medical history, prior treatment), examinations for eye disorders, belantamab mafodotin administration status

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication, dosage and administration, with approval conditions shown below, provided that the necessary precautions are included in the package insert and information about proper use of the product is appropriately disseminated in the post-marketing setting, and provided that the product is used in compliance with the proper-use guidelines under the supervision of a physician with sufficient knowledge and experience in treating hematopoietic malignancies in collaboration with an ophthalmologist at a medical institution capable of providing adequate emergency medical care. As the product is designated as an orphan drug, the re-examination period is 10 years.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

In combination with bortezomib and dexamethasone:

The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg administered as an intravenous infusion over at least 30 minutes every 3 weeks. The dose should be reduced depending on the patient's condition.

In combination with pomalidomide and dexamethasone:
The usual adult dosage is belantamab mafodotin (genetical recombination) 2.5 mg/kg for the first dose and 1.9 mg/kg for the second dose, administered as an intravenous infusion over at least 30 minutes every 4 weeks. The dose should be reduced depending on the patient's condition.

Approval Conditions

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

Warnings

1. Administration of belantamab mafodotin should be limited to patients for whom belantamab mafodotin treatment is deemed appropriate by a physician with sufficient knowledge and experience in treating hematopoietic malignancies at a medical institution capable of providing adequate medical care. Treatment must be initiated only after the patient or the family has provided consent after being fully informed of the efficacy and risks of belantamab mafodotin.
2. Eye disorders such as visual acuity reduced have been frequently reported. There have been cases where superficial punctate keratopathy, etc. appeared first and then progressed to serious eye disorders such as corneal ulcer. Belantamab mafodotin should be used in collaboration with ophthalmologists. Before the start of treatment with belantamab mafodotin, the patient must be examined by an ophthalmologist. Ophthalmologic examinations including a visual acuity test and slit lamp examination must be performed by an ophthalmologist before each of the first 4 doses of belantamab mafodotin in addition to the examination before the start of treatment. Thereafter, ophthalmologic examinations before subsequent doses should be conducted where deemed necessary. The patient's condition should be closely monitored. If any abnormality is noted, appropriate measures such as treatment discontinuation should be taken and the patient should undergo an assessment by the ophthalmologist.

Contraindication

Patients who have a history of hypersensitivity to any ingredient of the product

Precautions Concerning Indication

1. Eligible patients for belantamab mafodotin must have received at least 1 prior line of standard of care therapy, and MM is non-responsive to the therapy or relapsed after treatment.
2. Whether a patient is eligible for treatment with belantamab mafodotin should be decided by physicians who are fully familiar with prior therapy and other details of patients enrolled in the clinical studies presented in the "Clinical Studies" section, and have a thorough understanding of the efficacy and safety of belantamab mafodotin.

Precautions Concerning Dosage and Administration

1. The antineoplastic agent to be co-administered with belantamab mafodotin should be used only after becoming fully familiar with the details in the “Clinical Studies” section.
2. For patients on combination therapy with belantamab mafodotin, bortezomib, and dexamethasone, administration of belantamab mafodotin alone should be continued after the end of the combination therapy.
3. If the patient develops an adverse drug reaction following administration of belantamab mafodotin, the dose of belantamab mafodotin must be interrupted, reduced, or treatment must be discontinued based on the following guidelines.

Table 1. Dose levels for adverse drug reductions

	In combination with bortezomib and dexamethasone	In combination with pomalidomide and dexamethasone
Usual dose	2.5 mg/kg every 3 weeks	2.5 mg/kg for the first dose. For the second and subsequent doses, 1.9 mg/kg every 4 weeks
Dose reduction by 1 level	1.9 mg/kg every 3 weeks	1.9 mg/kg every 8 weeks
Dose reduction by 2 levels	Not applicable	1.4 mg/kg every 8 weeks

Table 2. Dose interruption, reduction, and treatment discontinuation guidelines for adverse drug reactions

Adverse drug reaction	Severity[Note 1)]	Action
Corneal examination findings and vision change[Note 2)]	Grade 1: Corneal examination findings Mild[Note 3)] superficial punctate keratopathy (documented worsening from baseline, with or without symptoms) Change in BCVA See Grade 1 in Table 3	Continue treatment.
	Grade 2: Corneal examination findings Moderate[Note 3)] superficial punctate keratopathy, patchy microcyst-like deposits, peripheral sub-epithelial haze, or a new peripheral stromal opacity Change in BCVA See Grade 2 in Table 3	Withhold treatment until both corneal examination findings and BCVA resolve to Grade ≤1. After resolution, resume treatment at a dose reduced by 1 level.[Note 4)]
	Grade 3: Corneal examination findings Severe[Note 3)] superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, central sub-epithelial haze, or a new central stromal opacity Change in best corrected visual acuity See Grade 3 in Table 3	
	Grade 4: Corneal examination findings Corneal epithelium defect Change in BCVA See Grade 4 in Table 3	Consider treatment discontinuation. If treatment is to be continued,[Note 5)] withhold treatment until both corneal examination findings and change in BCVA resolve to Grade ≤1. • In combination with Bd: after resolution, treatment may be resumed at a dose reduced by 1 level. • In combination with Pd: after resolution, treatment may be resumed at a dose reduced by 2 levels. Treatment must be discontinued if the event does not resolve and symptoms worsen after adequate action has been taken.
Platelet count decreased	Grade 3	Without bleeding: • At 2.5 mg/kg: reduce the dose to 1.9 mg/kg, and continue treatment.[Note 6)] • At ≤1.9 mg/kg: continue treatment at the same dose level.[Note 6)] With bleeding: • Withhold treatment until resolution to Grade ≤2. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Withhold treatment until resolution to Grade ≤3. Consider resuming treatment only if there is no bleeding after resolution: • At 2.5 mg/kg: resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: resume treatment at the pre-interruption dose level. • If platelet count decreased is considered to be related to multiple myeloma, without bleeding, and resolves with transfusion to 25,000/μL, treatment may be resumed at the pre-interruption dose level.
Infusion reaction	Grade 2	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume at a reduced infusion rate (no more than half the rate at which the symptoms initially appeared). Consider prophylactic medication when resuming infusion and for subsequent infusions.

	Grade 3	Interrupt infusion and provide appropriate treatment. After the symptoms resolve to Grade ≤1, resume infusion at a rate 1/4 to 1/8 of the rate at which the symptoms initially appeared. Consider prophylactic medication when resuming infusion. For subsequent infusions, prophylactic medication should be administered.
	Grade 4	Discontinue treatment.
Other adverse drug reactions	Grade 3	Withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.
	Grade 4	Consider treatment discontinuation. If treatment is to be continued, withhold treatment until resolution to Grade ≤1. • At 2.5 mg/kg: after resolution, resume treatment at 1.9 mg/kg. • At ≤1.9 mg/kg: after resolution, resume treatment at the pre-interruption dose level.

Note 1) With the exception of corneal examination findings and vision change, adverse drug reactions were graded according to CTCAE v. 5.0.
Note 2) Examination results may differ between the left and right eyes. The severity should be determined based on the most severe corneal findings or vision change in either eye.
Note 3) For the assessment of superficial punctate keratopathy, see the relevant materials provided by the marketing authorization holder.
Note 4) For combination therapy with pomalidomide and dexamethasone: if an adverse drug reaction occurs before the second dose, 1.9 mg/kg should be administered every 4 weeks from the second dose onward.
Note 5) The necessity of continuing treatment must be determined carefully based on the patient's condition. If treatment is to be continued, proper ocular management must be implemented.
Note 6) For combination therapy with bortezomib and dexamethasone: if the decreased platelet count resolves to Grade ≤2, the original dose level may be used.

Table 3. Severity of change in best corrected visual acuity due to eye disorder

Baseline best corrected visual acuity	Grade 1	Grade 2	Grade 3	Grade 4
1.5	1.2	0.8-1.0	0.1-0.7	<0.1
1.2	1.0	0.6-0.9	0.1-0.5	<0.1
1.0	0.8-0.9	0.5-0.7	0.1-0.4	<0.1
0.9	0.6-0.8	0.4-0.5	0.1-0.3	<0.1
0.8	0.6-0.7	0.4-0.5	0.1-0.3	<0.1
0.7	0.5-0.6	0.3-0.4	0.1-0.2	<0.1
0.6	0.5	0.3-0.4	0.1-0.2	<0.1
0.5	0.4	0.3	0.1-0.2	<0.1
0.4	0.3	0.2	0.1	<0.1
0.3	—	0.2	0.1	<0.1
0.2	—	0.1	—	<0.1

4. Make sure to confirm the results of ophthalmologic examinations (corneal examination findings and vision change) which are to be performed before each of the first 4 doses of belantamab mafodotin, and on an as-needed basis thereafter, to assess the severity and determine the dose level, taking ocular symptoms into account. Because examination results may differ between the left and right eyes, the severity should be determined based on the most severe corneal findings or vision change in either eye. If any vision change is noted, its association with belantamab mafodotin should be clarified. If the dose of belantamab mafodotin is reduced due to corneal findings or vision change, the dose should not be re-escalated.

Appendix

List of Abbreviations

ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cell-mediated phagocytosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
application	application for marketing approval
APRIL	a proliferation-inducing ligand
APTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	area under concentration-time curve
$AUC_{0\text{-}168}$	AUC from time zero to 168 hours
$AUC_{0\text{-}last}$	AUC from time zero to the last measurable time
AUC_{tau}	AUC over the dosing interval
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
BCRP	breast cancer resistance protein
BCVA	Best corrected visual acuity
Bd	bortezomib and dexamethasone
belantamab mafodotin	belantamab mafodotin (genetical recombination)
belantamab mafodotin/Bd	Combination of belantamab mafodotin, BOR, and DEX
belantamab mafodotin/Pd	Combination of belantamab mafodotin, POM, and DEX
BMI	body mass index
BOR	bortezomib
BSEP	bile salt export pump
C_{ave}	average concentration
CFZ/Ld	Combination regimen consisting of carfilzomib, LEN, and DEX
[redacted]	[redacted]
CHO	Chinese hamster ovary
CI	confidence interval
[redacted]	[redacted]
CL	total body clearance
C_{max}	maximum concentration
COVID-19	coronavirus disease
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRP	C-reactive protein
CRT	calreticulin
CTCAE	Common Terminology Criteria for Adverse Events
cys-mcMMAF	Cysteine maleimidocaproyl MMAF
DAR	daratumumab
DAR/Bd	combination therapy of daratumumab (DAR), bortezomib (BOR) and dexamethasone (DEX)
DAR/Ld	combination therapy of daratumumab (DAR), lenalidomide (LEN), and dexamethasone (DEX)
DEX	dexamethasone
DLBCL	diffuse large B-cell lymphoma

DLT	dose limiting toxicity
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response
DREAMM-1 study	Study BMA117159
DREAMM-2 study	Study 205678
DREAMM-3 study	Study 207495
DREAMM-6 study	Study 207497
DREAMM-7 study	Study 207503
DREAMM-8 study	Study 207499
DREAMM-11 study	Study 207504
DREAMM-12 study	Study 209626
ECL	electrochemiluminescence
EDTA	Ethylenediaminetetraacetic acid
EEA	early endosomal antigen
eGFR	estimated glomerular filtration rate
EHA	European Hematology Association
EIPA	5-(N-Ethyl-N-isopropyl)amiloride
ELISA	enzyme-linked immunosorbent assay
EPCB	end of production cell bank
ESMO	European Society of Medical Oncology
FcRn	neonatal Fc receptor
FcγR	Fcγ receptor
FL	follicular lymphoma
FMO	flavin-containing monooxygenase
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transpeptidase
HCEC	Human corneal epithelial cells
HCP	Host cell protein
hERG	human *ether-a-go-go* related gene
HMGB1	high-mobility group box 1
[redacted]	[redacted]
HSP70	heat shock protein70
HSP90α	heat shock protein90α
ICH Q5A (R1) guideline	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q5A (R1) guideline; “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B guideline	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q5B guideline; “Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products” (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D guideline	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q5D guideline; “Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products” (PMSB/ELD Notification No. 873, dated July 14, 2000)
ICH Q5E guideline	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q5E guideline; “Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process” (PFSB/ELD Notification No. 0426001, dated April 26, 2005)
IDMC	Independent Data Monitoring Committee

IFN	Interferon
Ig	Immunoglobulin
iGFR	individual glomerular filtration rate
IL	Interleukin
ILD	interstitial lung disease
IMWG	International Myeloma Working Group
ITT	intent-to-treat
KC/GRO	Keratinocyte chemoattractant/growth regulated oncogene
KIM-1	kidney injury molecule-1
KVA	Keratopathy Visual Acuity
LC-MS/MS	liquid chromatography-tandem mass spectrometry
Ld	Lenalidomide and dexamethasone
[redacted]	[redacted]
LEN	lenalidomide
M:E	Myeloid: Erythroid
MALDI-MSI	Matrix assisted laser desorption/ionization mass spectrometry imaging
MATE	multidrug and toxin extrusion
MCB	Master cell bank
MCH	mean corpuscular hemoglobin
mcMMAF	Maleimidocaproyl MMAF
MCP-1	Monocyte chemotactic protein-1
M-CSF	macrophage-colony stimulating factor
MCV	Mean Corpuscular Volume
MDCKII	Madin-Darby canine kidney type II
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMAE	monomethyl auristatin E
MMAF	Monomethyl auristatin F
MRD	Minimal residual disease
mRNA	messenger ribonucleic acid
MRP	multidrug resistance-associated protein
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
nano-LC-MS	Nano-liquid chromatography-mass spectrometry
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology, Multiple myeloma
NCI-PDQ	National Cancer Institute Physician Data Query
NFAT	Nuclear factor of activated T-cells
NF-κB	Nuclear factor κ B
NK	Natural killer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PAR	Proven acceptable range
PBMC	peripheral blood mononuclear cell
PBS	phosphate buffer saline
Pd	pomalidomide and dexamethasone
PFS	progression-free survival
P-gp	P-glycoprotein
PI	propidium iodide
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
POM	pomalidomide
PPK	population pharmacokinetics

PR	partial response
PT	preferred term
[redacted]	[redacted]
Q3W	once every 3 weeks
Q4W	once every 4 weeks
QD	quaque die
QT	QT interval
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
QW	once every week
RDW	red blood cell distribution width
R-ISS	Revised International Staging System
RMP	Risk Management Plan
RPA-1	Renal Papillary Antigen 1
RPTEC	Renal proximal tubule epithelial cells
RT-qPCR	Reverse transcription - quantitative polymerase chain reaction
sBCMA	Soluble BCMA
SCID mouse	severe combined immunodeficient mouse
sCR	stringent complete response
[redacted]	[redacted]
SIMS	Secondary ion mass spectrometry
SMQ	Standardized Medical Dictionary for Regulatory Activities query
SOC	system organ class
SPR	surface plasmon resonance
$t_{1/2}$	elimination half-life
[redacted]	[redacted]
TFN-α	Tumour necrosis factor alpha
t_{max}	time to reach maximum concentration
total mAb	anti-BCMA antibody with or without MMAF
TTR	Time to response
UDPGA	uridine diphosphate glucuronic acid
V1	central volume of distribution
V2	peripheral volume of distribution
VGPR	very good partial response
VPd	bortezomib, pomalidomide and dexamethasone
WCB	Working cell bank
αGST	alpha-glutathione S-transferase