December 6, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products 1. Human somatic cell-processed product
Non-proprietary Name	Idecabtagene Vicleucel
Brand Name	Abecma Intravenous Infusion
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 31, 2021 (Application for marketing approval)

Results of Deliberation

In the meeting held on December 6, 2021, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The conditional and time-limited approval is not applicable to the product. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

November 17, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Abecma Intravenous Infusion
Classification	Human Cellular/Tissue-based Products 1. Human somatic cell-processed product
Non-proprietary Name	Idecabtagene Vicleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 31, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous peripheral blood mononuclear cells (PBMCs) isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA) is introduced by using a recombinant lentiviral vector.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 12 of 2019 [*31 sai*]; PSEHB/MDED Notification No. 1125-2 dated November 25, 2019, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare [MHLW])
Reviewing Office	Office of Cellular and Tissue-based Products

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 or performance as well as dosage and administration or method of use shown below, with the following approval conditions.

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Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-cluster of differentiation (CD)38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc., for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450×10^6 cells (range, 280×10^6-540×10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Attachment

Review Report (1)

September 17, 2021

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	Abecma Intravenous Infusion
Classification	Human Cellular/Tissue-based Products 1. Human somatic cell-processed product
Non-proprietary Name	Idecabtagene Vicleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 31, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous peripheral blood mononuclear cells (PBMCs) isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets B cell maturation antigen (BCMA) is introduced by using a recombinant lentiviral vector.

Proposed Indication or Performance

Relapsed or refractory multiple myeloma

Abecma should be used only in patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-cluster of differentiation (CD)38 monoclonal antibody.

Proposed Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected.
2. Transportation of leukapheresis material
   The leukapheresis material is packed and transported under refrigerated conditions to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and keeping of Abecma
   Abecma is received in a frozen condition and cryopreserved until immediately before use.
4. Treatment before Abecma administration
   Administer a lymphodepleting chemotherapy regimen.
   1) Administer cyclophosphamide (anhydrate) 300 mg/m^2 and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
   2) Abecma is infused 3 days after the completion of lymphodepleting chemotherapy.

5. Infusion of Abecma

Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 150 × 10^6-540 × 10^6 cells) of chimeric antigen receptor (CAR)-expressing T cells (irrespective of body weight), administered intravenously as a single dose. Refer to the Release for Infusion Certificate for the actual cell count and dose.

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

Idecabtagene vicleucel (hereinafter referred to as "Abecma") is a regenerative medical product consisting of a patient's own peripheral T cells that have been cultured and proliferated through transduction with genetically modified lentiviral vector containing chimeric antigen receptor (CAR) that specifically recognizes B cell maturation antigen (BCMA). Abecma is intravenously administered into the patient to obtain a therapeutic effect based on the pharmacological action, in the same manner as drugs.

The CAR that is transfected into Abecma is comprised of a murine single-chain variable fragment (scFv) specifically recognizing B cell maturation antigen (BCMA), a human CD8α hinge and transmembrane domain fused to the intracellular signaling domains of human 4-1BB and CD3ζ. When recognizing BCMA-expressing cells, Abecma induces the activation and proliferation of the genetically modified T cells, thereby obtaining effector functions such as a cytopathic effect. Through these actions, Abecma is expected to kill BCMA-positive tumor cells.

Abecma was designated as an orphan regenerative medical product with the intended indication or performance for treatment of "relapsed or refractory multiple myeloma" on November 25, 2019 (Orphan Regenerative Medical Product Designation No. 12 of 2019 [*31 sai*]).

1.2 Development history etc.

Multiple myeloma (MM) is a tumor that arises from malignant transformation of plasma cells, a type of cells differentiated from B lymphocytes. The disease is characterized by monoclonal immunoglobulin (M-protein) in serum or urine, which is produced by myeloma cells and by a variety of clinical symptoms including hematopoietic disorder principally involving anemia, renal disorder, and osteolytic lesion (Guidelines for Diagnosis and Management of Multiple Myeloma [in Japanese], fifth edition, 2020; Bunkodo Co., Ltd., p.2).

MM, even if it responds to the initial treatment, relapses eventually with the malignancy increasing with repeated treatments, resulting in a shorter period before progressive disease (PD). The diseases ultimately progress to refractory MM with poor outcome. Worse, the risk of complications associated with the treatment and the disease increases with repeated treatments. No standard treatment is available for MM that has become relapsed or refractory after treatments with an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

The development of Abecma was initiated in 20[redacted] by bluebird bio, Inc., and developed jointly with Celgene Corporation from 20[redacted]. A foreign phase I study (Study CRB-401) in patients with relapsed or refractory MM was started in January 2016. Then, a global phase II study (Study MM-001) in patients with relapsed or refractory MM was conducted from [redacted] 20[redacted].

Abecma was approved in the US in March 2021 with Study MM-001 as the pivotal study for the indication or performance of "ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or

refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody."

In Europe, Abecma was approved in August 2021 with Study MM-001 as the pivotal study for the indication or performance of "Abecma is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy."

In Japan, patient enrollment in Study MM-001 was initiated by Celgene Corporation in [redacted] 20[redacted].

Recently, a marketing application for Abecma was submitted with the results of Studies CRB-401 and MM-001 as pivotal data.

Celgene Corporation submitted the application for Abecma. After the merge of Celgene Corporation with Bristol-Myers Squibb K.K. in July 2021, development of Abecma was transferred to Bristol-Myers Squibb K.K. during the application.

2. Quality and Outline of the Review Conducted by PMDA

Abecma is prepared from T cells isolated from a patient's own PBMC via a leukapheresis procedure. The obtained cells are enriched for T cells, which are then transduced with viral vector containing a transgene encoding CAR directed against human BCMA. The transduced T cells are expanded in culture.

2.1 Viral vector

The gene transfer vector is a lentiviral vector that is derived from human immunodeficiency virus (HIV)-1 and has genetically modified self-inactivating (SIN) long terminal repeat (LTR), which deprives the vector of replication competence. The anti-BCMA chimeric antigen receptor (anti- BCMA CAR) gene transferred by the viral vector includes sequences encoding the scFv region of the anti-BCMA mouse monoclonal antibody C11D5.3, human CD8α hinge and transmembrane domain fused to the intracellular signaling domains of human 4-1BB and human CD3-ζ.

The viral vector genome is composed of HIV-1-derived 5' LTR, packaging signal (Ψ), [redacted], [redacted], [redacted], anti-BCMA CAR transgene, [redacted], and [redacted] 3' LTR. Most of the HIV-1 genome is deleted. Components required for the production of the viral vector were divided into 3 plasmid vectors (i.e., Gag/Pol, Rev, and glycoprotein of the vesicular stomatitis virus [VSV-G]), in order to minimize homologous recombination and thereby to prevent the emergence of a replication competent lentivirus.

2.1.1 Plasmids

The viral vector is generated from the transfer plasmid and 3 helper plasmids. Under the control of [redacted], each plasmid contains either anti-BCMA CAR, Gag/Pol, Rev, or VSV-G. The control items of the plasmids include [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], bacterial endotoxins, and sterility.

2.1.2 Generation and control of cell substrate for production of viral vector

The viral vector is produced using human embryonic kidney 293T (HEK293T cells). HEK293T cells ([redacted]) obtained from the American Type Culture Collection (ATCC) were used to generate master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and end of production cells (EPC) were subjected to characterization and purity tests in accordance with the ICH Q5A (R1) and Q5D guidelines. Table 1 shows tests performed for adventitious agents. The results demonstrated that neither viral nor non-viral adventitious agents were detected by any of the tests.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. A new MCB will not be prepared, but a new WCB will be prepared as necessary.

Table 1. Tests for adventitious agents

In vitro virus tests[*1]
In vivo virus tests (suckling mice, mature mice, guinea pigs, and embryonated hen's eggs)
Murine antibody production tests
Bovine virus tests (HA and CPE,[*2] immunofluorescence staining [BVDV, BAV, BPV, BRSV, Reo, BTV, and RABV])
Porcine virus tests (HA and CPE [Vero cells and PK15 cells], immunofluorescence staining [TGEV, PAV, PPV, and PHEV])
In vitro human virus tests (HTLV-1, HTLV-2, HIV-1, HIV-2, HBV, HCV, HHV-6, HHV-7, HHV-8, CMV, EBV, and PVB19)
Transmission electron microscopy
Reverse transcriptase activity test
PCR (GALV, amphotropic)
Sterility
Mycoplasma test

*1 Indicator cells used were [redacted] cells, [redacted] cells, and [redacted] cells for MCB, and [redacted] cells, [redacted] cells, and [redacted] cells for WCB and EPC.
*2 Indicator cells used were [redacted] cells and [redacted] cells for MCB, and [redacted] cells and [redacted] cells for WCB and EPC.

2.1.3 Manufacturing process of viral vector

The manufacturing process of the viral vector consists of [redacted], [redacted], [redacted] and [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted], filling and testing.

Critical steps include [redacted] and [redacted], [redacted], [redacted], and [redacted], [redacted] and [redacted].

Process validation of the manufacturing process of the viral vector has been implemented at the commercial production scale.

2.1.4 Safety evaluation of adventitious agents in the viral vector

Table 2 shows raw materials of biological origin other than HEK293T cells used in the manufacturing process of the viral vector, all of which except for fetal bovine serum (FBS) (a) meet the Standards for Biological Ingredients.

FBS (a) used for the preparation of MCB is derived from the blood of healthy cattle that originated in Canada and the US. The manufacturing process of MCB does not include evaluation for viral inactivation/removal but includes filtration process for removal of pathogen. Also, the following tests

are conducted: Adventitious bovine virus test, bacterial endotoxin test, sterility test, and mycoplasma test. In addition, bovine virus test was conducted on MCB prepared by using said FBS, as shown in Table 1. Results have confirmed that no virus of bovine origin was detected. The bovine blood used as a source material for MCB was collected in Canada or in the US before 2013 when the US was certified by the International Epizootic Office (OIE) as a country with negligible risk of transmission of the pathogen for bovine spongiform encephalopathy (BSE). Also, the bovine blood used as a source material for MCB has been confirmed to fulfill the guide for ensuring the certain safety against BSE as a result of the evaluation according to "Handling of Risk Evaluation, etc. in Applications for Partial Changes in Pharmaceuticals or Medical Devices Using Bovine-derived Raw Materials [in Japanese]" (PFSB/ELD Notification No. 0801001 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and PFSB/SD Notification No. 0801001 of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 1, 2003).

Table 2. Raw materials of biological origin other than HEK293T cells

Raw material name	Animal	Material	Process
FBS (a)	Cattle	Blood	Generation of MCB
FBS (b)	Cattle	Blood	[redacted], [redacted], [redacted], and [redacted]
Casein hydrolysate	Cattle	Milk	[redacted]
HSA	Human	Blood	[redacted]

[redacted] after the viral vector production is tested for adventitious agents as a specification for the viral vector, as shown in Section 2.1.7.

2.1.5 Manufacturing process development of viral vector

The main changes in the manufacturing process of the viral vector during the development are shown below. Table 3 shows viral vector manufacturing process employed in the manufacture of the formulation used in each non-clinical and clinical study.

- From Process A to Process B: Changes in [redacted] and [redacted]
- From Process B to Process C (proposed process): Change in [redacted], addition of [redacted], and change in [redacted]

In association with these changes of the manufacturing process of the viral vector, the quality attributes of the pre-and post-change viral vector were compared and shown to be comparable.

The manufacturing process development employs the quality by design (QbD) concept.

Table 3. Viral vector manufacturing process employed in the manufacture of the formulation used in each non-clinical and clinical study

Manufacturing process	Non-clinical studies and clinical studies
Process A	Studies [redacted], [redacted], and [redacted]
Process B	Studies [redacted], [redacted], and [redacted]
Process C (proposed process)	—

2.1.6 Characterization of viral vector

2.1.6.1 Structure and characterization

Table 4 shows characterizations performed.

Table 4. Characterization items

Tests on viral vector	Structural protein and enzyme proteins (VSV-G, reverse transcriptase, integrase, Gag polyprotein and its degradation products [, , ,]), , , impurities (Impurity A [ ], RCL, plasmid DNA, host cell DNA [, and , and], host cell protein, residual Impurity B, residual Impurity C)
Characterization of component cells of Abecma genetically modified by viral vector	, , , , gene insertion site analysis of viral vector [see Section 5.2.1]

2.1.6.2 Product/process-related impurities

Impurity A ( ) and replication competent lentivirus (RCL) were identified as product-related impurities. Plasmid DNA, host cell DNA (genomic DNA [gDNA]), host cell protein, Impurity B, and Impurity C were identified as process-related impurities. All process-related impurities have been demonstrated to be adequately removed by the manufacturing process. , , ,), and are controlled by the specifications for the viral vector. RCL expression has not been observed in batches manufactured to date.

2.1.7 Control of viral vector

The proposed specifications for the viral vector include description, identification (method and method), , , , purity (,], and), bacterial endotoxins, mycoplasma (test on unpurified bulk harvest), sterility, RCL (and), virus tests (adventitious virus tests on [and *in vitro* virus tests (, , , , and cells)]), , titer (in transduced cells against), and biological activity (of anti-BCMA CAR-expressing T cells).

2.1.8 Stability of viral vector

Table 5 shows a summary of major stability studies for the viral vector.

Table 5. Summary of major stability studies for the viral vector

Study	Manufacturing process	Number of batches	Storage condition	Study period	Storage form
Long-term testing	Process A	3	°C	months	vial with rubber stopper
	Process B	4		months[*1]	
	Proposed process	5		months[*2]	
Accelerated testing	Proposed process	4	°C	months	
Stress testing	Proposed process	1	°C		
		1	°C		
		1			

*1

*2

The long-term testing (°C) showed no clear changes in quality attributes throughout the study period.

The accelerated testing ([redacted]°C) showed a tendency of an increase in [redacted], [redacted], and tendencies of a decrease in biological activity ([redacted] of anti-BCMA CAR-expressing T cells) and titer ([redacted] due to gene transduction).

The stress testing ([redacted]°C) showed tendencies of a decrease in [redacted], the biological activity ([redacted] of anti-BCMA CAR-expressing T cells) and titer ([redacted] due to gene transduction).

The stress testing ([redacted]°C) showed a decrease in titer ([redacted] due to gene transduction) at time point of [redacted], in addition to the changes observed in the stress testing ([redacted]°C).

The stress testing ([redacted]) showed tendencies of a decrease in [redacted], the biological activity ([redacted] of anti-BCMA CAR-expressing T cells), and titer ([redacted] due to gene transduction).

The above testing indicated a proposed shelf life of [redacted] months for the viral vector when stored at [redacted] in a [redacted] vial sealed with a [redacted] rubber stopper.

2.2 Product

2.2.1 Description and composition of product and formulation development

The product contains component cells including anti-BCMA CAR-expressing T cells at the count in each ethylene vinyl acetate (EVA) cryopreservation bag[1)] as specified in Dosage and Administration or Method of Use. Excipients contained in the product include Plasma-Lyte A and CryoStor CS10.

2.2.2 Manufacturing process

The manufacturing process of the product includes [redacted], [redacted] and [redacted], [redacted] and [redacted], [redacted], [redacted], [redacted], [redacted] and [redacted], [redacted], filling/labeling, packaging/freezing/storage/testing, and storage.

Critical steps include [redacted], [redacted], and [redacted].

Process validation of the manufacturing process for the product was conducted at commercial scale.

2.2.3 Safety evaluation of adventitious agents

2.2.3.1 Patient's peripheral blood mononuclear cells

A patient's own peripheral blood mononuclear cells, which serve as a raw material of the product, conform to requirements for the collection method and documentation defined in the Human Cell and Tissue Raw Material Standards under the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210 of 2003). Before apheresis, the patient undergoes an interview at the medical institution and, if necessary, is tested for serological tests (cytomegalovirus [CMV], hepatitis B virus [HBV], hepatitis C virus [HCV], and HIV).

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1) Bags with 3 different volumes (50 mL, 250 mL, and 500 mL) filled with 10 to 30 mL, 30 to 70 mL, and 55 to 100 mL, respectively, of the cell suspension.

2.2.3.2 Raw materials of biological origin other than patient's peripheral blood mononuclear cells

Table 6 shows raw materials of biological origin, etc. (other than patient's peripheral blood mononuclear cells) used in the manufacturing process. All of these raw materials were confirmed to conform to the Standards for Biological Ingredients.

Table 6. Raw materials of biological origin, etc., other than patient's peripheral blood mononuclear cells used in the manufacturing process

Raw material name	Animal	Origin or material	Process
HSA	Human	Blood	Component of [redacted], [redacted] and [redacted], and [redacted] (used for [redacted] and [redacted], [redacted], and [redacted])
Human [redacted] serum	Human	Blood	Component of [redacted] (used for [redacted] and [redacted], [redacted], and [redacted])
Bovine thrombin	Cattle	Plasma and lung	[redacted]
Human transferrin	Human	Blood	Component of [redacted] (used for [redacted] and [redacted], [redacted], and [redacted])
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]

2.2.4 Manufacturing process development

Table 7 shows main changes in the development process of the product. Table 8 shows manufacturing processes of the product used in non-clinical and clinical studies. The product manufactured by Process V is used for the commercial product.

In association with these changes of the manufacturing process, the quality attributes of the pre-and post-change product were compared and shown to be comparable.

The manufacturing process development employs the QbD concept.

Table 7. Changes of manufacturing process of the product

Manufacturing process	Changes, etc.
From Process I to Process II	Addition of [redacted]
From Process II to Process III	Changes in [redacted], and [redacted] and [redacted], change in [redacted], and change in [redacted]
From Process III to Process IV	Addition of [redacted], change in [redacted], addition of [redacted], change in [redacted]
From Process IV to Process V (proposed process)	Addition of [redacted], deletion of [redacted], addition of [redacted], deletion of [redacted]

Table 8. Manufacturing process of the formulation used in non-clinical and clinical studies

Manufacturing process	Non-clinical studies and clinical studies
Process I	Studies [redacted] and [redacted]
Process II	Studies [redacted] and [redacted]
Process III	Studies [redacted], [redacted], and [redacted]
Process IV	Studies [redacted] and [redacted]
Process V (proposed process)	—

2.2.5 Characterization

2.2.5.1 Structure and characterization

Characterization was performed as shown in Table 9.

Table 9. Characterization of component cells

Structure and cytological properties	Primary amino acid sequence of anti-BCMA CAR protein, transduction rate, transgene copy number, gene insertion site analysis of viral vector [see Section 5.2.1], T-cell subset analysis (, , , and)
Biological properties	BCMA-binding activity, BCMA-specific T cell activation, cytokine release in response to BCMA-specific stimulation (, , , , and), BCMA-specific and , BCMA-specific cytotoxic activity, BCMA-induced ,
Purity	Cell viability, non-target cells (, , , , , , , , , ,), residual viral vector, protein, plasmid DNA, host cell DNA (gDNA), host cell protein, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, and Impurity L

2.2.5.2 Process-related impurities

Process-related impurities include residual viral vector, protein, plasmid DNA, host cell DNA (gDNA), host cell protein, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, and Impurity L.

The process-related impurities, except for residual viral vector, are unlikely to raise safety concerns in humans based on the estimated exposure per dose, calculated from the estimated residual amount of impurity in the product. Therefore, control items for process-related impurities have not been specified.

The capacity to remove residual viral vector was subjected to process evaluation for Processes III and IV, and the amount in the final product has been demonstrated to be below the lower limit of quantitation (/mL). The proposed process, Process III, and Process IV were shown to have a comparable capacity to remove the viral vector.

2.2.6 Control of product

The proposed specifications for the product include description, identification (method), purity (, , and), bacterial endotoxins, sterility, mycoplasma, , biological activity ( ), and content (number of anti-BCMA CAR-expressing T cells).

2.2.7 Stability of product

Table 10 shows a summary of major stability studies for the product.

Table 10. Summary of major stability studies for the product

Study	Number of batches	Manufacturing process	Origin	Storage condition	Study period	Storage form	Filled volume/ bag volume
Long-term testing	3	Process III	Healthy adults	≤-130°C	[redacted] months	EVA cryopreservation bag	[redacted] mL
	3				12 months[*1]		[redacted] mL
	3				[redacted] months		[redacted] mL
	3				[redacted] months	[redacted] vial with [redacted] rubber stopper	[redacted] mL
	3	Process IV			12 months	EVA cryopreservation bag	[redacted] mL
	3[*2]				12 months		[redacted] mL
	3				12 months		[redacted] mL
	2[*3]				[redacted] months		[redacted] mL
	3	Process V (proposed process)			[redacted] months[*4]		[redacted] mL
Stress testing	3	Process III	Healthy adults	[redacted]		[redacted] vial with [redacted] rubber stopper	[redacted] mL
	3		Patients				[redacted] mL
In-use stability testing	3		Healthy adults	RT	[redacted]	EVA cryopreservation bag	[redacted] mL
	3						[redacted] mL
	3						[redacted] mL

*1 Data are available for 12 months in 1 batch and for [redacted] months in 2 batches.
*2 The site of the preparation process for PBMC was different from that in process IV.
*3 Manufactured using [redacted].
*4 The stability study is ongoing for up to 12 months.

The long-term testing showed no clear changes in quality attributes throughout the study period.

The stress testing showed decreased [redacted], [redacted], and [redacted].

The in-use stability testing showed tendencies of a decrease in [redacted] and [redacted] at [redacted] after thawing.

On the basis of the above, a shelf life of 12 months has been proposed for the product when stored in EVA cryopreservation bags at ≤−130°C. Administration should be completed within 1 hour at room temperature after thawing.

2.3 QbD

The manufacturing process development employs the QbD concept, and the quality control strategy was designed based on the following investigations:

- Identification of critical quality attributes (CQAs):
  On the basis of the information obtained through the development of the product and related knowledge, etc., the following CQAs were identified regarding process-related impurities and product characteristics:
  - CQAs of viral vector
    [redacted], sterility, bioburden,

bacterial endotoxin, mycoplasmas, adventitious viruses, RCL, Impurity M, Impurity N, Impurity C, Impurity B, [redacted], and [redacted].

- CQAs of product
  Sterility, mycoplasma, bacterial endotoxin, RCL, [redacted], Impurity N, [redacted], Impurity M, Impurity C, [redacted], and Impurity B

- Process characterization:
  Process parameters were classified, and characterization of each process was performed by risk assessment based on their effect on CQA.
- Establishment of control method:
  On the basis of the knowledge on the process including the information obtained from the above process characterization, the method for controlling the quality attributes of the product was established by the combination of process parameter control, in-process control, and specifications. Results confirmed that the characteristics of the product are adequately controlled [see Section 2.2.5.2 for the control of process-related impurities].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the viral vector and of the product is controlled adequately.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the primary pharmacodynamics or performance of Abecma: *In vitro* studies, *in vivo* studies, and *in vivo* studies evaluating the anti-tumor effect of Abecma in NOD-Cg-Prkdc^{scid} IL2rg^{tm1Wjl}/SzJ (NSG) mice intravenously transplanted with human Burkitt's lymphoma (BL) cell line. Abecma used in each of these studies was manufactured from PBMC derived from healthy adults, using a downscaled Process [redacted] [see Section 2.2.4].

3.1 *In vitro* studies

3.1.1 Correlation of BCMA mRNA expression level and BCMA expression in target cells with Abecma-induced IFN-γ production (CTD 4.2.1.1.1)

BCMA mRNA expression level and BCMA antigen expression in various tumor cell lines were investigated by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) and by flow cytometry. Then, the amount of Abecma-induced interferon-gamma (IFN-γ) production was evaluated following cocultivation of each tumor cell line (5×10^4 cells) with Abecma (total number of T cells, 5×10^4) by enzyme-linked immunosorbent assay (ELISA).

Abecma-induced IFN-γ production was undetectable or barely detectable when co-cultivated with BCMA-non or -low expressing cell lines (myelogenous leukemia [ML]-derived K562 cells, acute lymphoblastic leukemia [ALL]-derived NALM-6 cells and NALM-16 cells, mantle cell lymphoma [MCL]-derived REC-1 cells, and Hodgkin lymphoma [HL]-derived HDLM-2 cells). In contrast,

Abecma-induced IFN-γ production was confirmed upon cocultivation with K562.BCMA(16) cells[2] and K562.BCMA(B5) cells[3] that were forced to express BCMA and in BCMA-expressing tumor cell lines (MM-derived RPMI-8226 cells, chronic lymphocytic leukemia (CLL)-derived MEC-1 cells, MCL-derived JeKo-1 cells, HL-derived RPMI-6666 cells, BL-derived Daudi cells, and Ramos cells) (Tables 11 and 12).

The above results showed that when tumor cell lines with different BCMA expression levels and Abecma were co-cultivated, the Abecma-induced IFN-γ production level correlated with BCMA mRNA expression level and with BCMA antigen expression.

Table 11. Correlation between Abecma-induced IFN-γ production and BCMA mRNA expression level in each type of cells

Tumor cell line		BCMA mRNA (ΔCt^*)	IFN-γ production (ng/mL)	
			n	Mean ± SE (individual value for n = 1)
K562 cells	ML cell line	12.0	1	0
HDLM-2 cells	HL cell line	11.4	1	0
NALM-16 cells	ALL cell line	6.6	1	0
NALM-6 cells	ALL cell line	5.4	1	0
JeKo-1 cells	MCL cell line	0.9	4	13.4 ± 1.7
MEC-1 cells	CLL cell line	1.0	6	16.1 ± 1.6
Daudi cells	BL cell line	1.3	6	36.0 ± 4.8
RPMI-6666 cells	HL cell line	0.1	6	32.5 ± 5.6

* Relative BCMA mRNA expression level measured by RT-qPCR as estimated from the difference in amplification cycle time compared with house-keeping gene

Table 12. Correlation between Abecma-induced IFN-γ production and BCMA expression in each type of cells

Tumor cell line		BCMA expression*		IFN-γ production (ng/mL)	
		n	Mean ± SE (individual value for n = 1)	n	Mean ± SE (individual value for n = 1)
K562 cells	ML cell line	12	0	1	0
K562.BCMA(16) cells	ML cell line	7	5061 ± 429	6	46 ± 5
K562.BCMA(B5) cells	ML cell line	12	76942 ± 6758	6	47 ± 3
NALM-6 cells	ALL cell line	3	0	1	0
NALM-16 cells	ALL cell line	3	0	1	0
REC-1 cells	MCL cell line	3	0	1	0
HDLM-2 cells	HL cell line	12	0	1	0
JeKo-1 cells	MCL cell line	5	222 ± 138	4	13 ± 2
Daudi cells	BL cell line	9	1173 ± 234	6	36 ± 5
RPMI-6666 cells	HL cell line	3	1219 ± 67	6	32 ± 6
Ramos cells	BL cell line	3	1713 ± 220	4	28 ± 6
MEC-1 cells	CLL cell line	3	3173 ± 351	6	16 ± 2
RPMI-8226 cells	MM cell line	3	12590 ± 1276	5	37 ± 3

* BCMA expression measured by flow cytometry using mouse anti-human BCMA monoclonal antibody, expressed as relative expression compared with an antibody with known binding number

3.1.2 BCMA-dependent cytotoxic effect of Abecma (CTD 4.2.1.1.1)

Abecma or bb612 cells,[4] the negative control, were co-cultivated with target cells shown below, and viable cells were counted by flowcytometry. The cytotoxic activity of Abecma was evaluated based on the ratio of viable cell count of BCMA-expressing cells to that of BCMA-non-expressing cells. Abecma did not show cytotoxic activity against non-BCMA-expressing K562 cells, but showed a cytotoxic activity

[2] Cell line obtained by cloning of cells with a medium expression of BCMA from among K562 cells transduced with BCMA gene
[3] Cell line obtained by cloning of cells with a high expression of BCMA from among K562 cells transduced with BCMA gene
[4] T cells expressing inactive CD19 CAR without signal transduction domain. The cells were manufactured using PBMC derived from healthy adults by Process [redacted] [see Section 2.2.4] at a reduced scale.

against K562-BCMA cells[5)] forcedly expressing BCMA and against BCMA-expressing, MM-derived RPMI-8226 cells, with the cytotoxic activity correlating with the ratio of effector T cell count to target tumor cell count (E/T ratio). In contrast, bb612 cells showed little cytotoxic activity against these cells.

- Abecma or bb612 cells were co-cultivated in a E/T ratio of 0.5, 1.7, or 5.0 with the target cell suspension consisting of mixture of K562 cells and K562-BCMA cells (1:1).
- Abecma or bb612 cells were co-cultivated in a E/T ratio of 0.7, 2.2, 6.7, or 20.0 with the target cell suspension consisting of mixture of K562 cells and RPMI-8226 cells (1:1).

3.1.3 BCMA-dependent growth of Abecma (CTD. 4.2.1.1.1)

Abecma was stained with CellTrace Violet, a cytoplasm fluorescent staining pigment, and cultivated alone or in combination with non-BCMA-expressing K562 cells (1:1) or with K562-BCMA cells forcedly expressing BCMA (1:1), and Abecma cell growth was evaluated by flowcytometry.[6)] Results showed that the cell growth occurred only under cocultivation with K562-BCMA cells.

3.2 *In vivo* studies

3.2.1 Evaluation of pharmacological activity of Abecma in NSG mice subcutaneously transplanted with human MM cell line (CTD 4.2.1.1.4)

Female NSG mice were subcutaneously transplanted with human MM-derived RPMI-8226 cells and, when the volume of the transplanted tumor tissue reached approximately 400 mm^3, a single dose of vehicle (culture medium), Abecma (1.0×10^7 T cells in total), or the negative control (bb612 cells[4)]) was administered intravenously (n = 10/group). Over 50 days starting from the day of administration (Day 1), anti-tumor activity,[7)] changes in body weight, and viability were evaluated in the vehicle group, the bb612 group, and the Abecma group. Neither the tumor tissue volume nor the body weight decreased in the vehicle group and the bb612 group (3.28×10^6 CAR-expressing T cells), and all of the test animals in both groups died of tumor-related death (humanitarian euthanasia) on or before Day 29, with the viability on Day 50 being 0%. In contrast, in the Abecma group (6.16×10^6 CAR-expressing T cells), the tumor tissue disappeared on or before Day 19 and body weight increased. The viability on Day 50 was 100%.

3.2.2 Evaluation of dose-dependent anti-tumor effect of Abecma in NSG mice subcutaneously transplanted with human MM cell line (CTD 4.2.1.1.5)

Female NSG mice were subcutaneously transplanted with human MM-derived RPMI-8226 cells and, when the volume of the transplanted tumor tissue reached approximately 130 mm^3, a single dose of vehicle (culture medium) or Abecma (containing 6.16 × 10-6.16×10^6 CAR-expressing T cells [total T cell count, 1.0×10^2-1.0×10^7]) was administered intravenously (n = 9/group). Over 23 days from the day of administration (Day 1), anti-tumor activity,[7)] changes in body weight, and viability were evaluated. In the vehicle group, body weight increased and the tumor tissue volume did not decrease. In contrast, the Abecma groups receiving $\geq 6.16 \times 10^5$ CAR-expressing T cells showed disappearance of the tumor tissue on or before Day 20, accompanied by a body weight increase. The highest dose group (6.16×10^6 cells) showed rapid shrinkage of the tumor tissue after administration of Abecma, achieving

5) Cell line generated by transduction of BCMA gene into ML-derived K562 cells
6) The cellular proliferative potency was assessed alternatively based on the phenomenon of 50% decrease in each cell division in the fluorescence intensity of the pigment incorporated into cells.
7) The antitumor effect was assessed based on the volume of the tissue consisting of the transplanted RPMI-8226 cells.

disappearance of the tumor tissue in 6 of 9 animals on Day 12 and in all animals on Day 20. In groups receiving 6.16×10 to 6.16×10^4 CAR-expressing T cells, no decrease in the tumor tissue was observed. All test animals in all treatment groups survived up to Day 23.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the efficacy of Abecma:

In vitro studies demonstrated that Abecma secreted IFN-γ in a BCMA-dependent manner and exhibited proliferative and cytotoxic activities. In *in vivo* studies, a single intravenous administration of Abecma to mice transplanted with BCMA-expressing human MM cell line exhibited an anti-tumor effect against BCMA-expressing tumor cells and prolonged the survival of the animals.

The above results suggest that Abecma recognizes MM cells in a BCMA-dependent manner, thereby exhibiting cytotoxic activity.

PMDA accepted the explanation of the applicant.

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

The applicant submitted the following data relating to the non-clinical biological disposition of Abecma.

Abecma used in this study was manufactured using PBMC derived from healthy adults by Process [redacted] [see Section 2.2.4] at a reduced scale.

4.1 Cellular kinetics/pharmacokinetics and *in vivo* distribution of Abecma in NSG mice subcutaneously transplanted with human MM cell line (CTD 4.2.2.7.1)

Female NSG mice were subcutaneously transplanted with human MM-derived RPMI-8226 cells and, when the volume of the transplanted tumor tissue reached approximately 150 mm^3, a single dose of Abecma (3×10^6 CAR-expressing T cells [total T cell count, 5.0×10^6]) was administered intravenously (n = 14). In a similar manner, female NSG mice not transplanted with tumor cell line (untreated mice) received a single dose of Abecma intravenously (n = 14). Over 29 days starting from the day of administration (Day 1), CD3-positive CAR-expressing T cell count and CD3-positive T cell count in peripheral blood were evaluated by flow cytometry, and the percentage[8)] of CD3-positive T cells in the tumor tissue by immunohistochemistry (IHC) method. The distribution of Abecma in the bone marrow, kidney, liver, lung, and spleen was evaluated based on the measurement of the percentage[8)] of CD3-positive T cells by IHC method. Soluble BCMA (sBCMA) concentration in serum was evaluated by ELISA, and the percentage[8)] of BCMA-expressing RPMI-8226 cells in the tumor tissue by IHC method.

In the untreated mice group, the mean CD3-positive CAR-expressing T cell count and the mean CD3-positive T cell count in the peripheral blood reached a peak level on Day 2 and decreased up to Day 29. CD3-positive T cells were barely detectable in the liver, kidney, and bone marrow (<1% of each of the entire tissue), reached a peak level on Day 8 and 15, respectively, in spleen and lung, but remained ≤25% of the entire tissue. No sBCMA was detected in serum.

8) Slide specimens of bone marrow, kidney, liver, lung, spleen, and tumor tissue were prepared, and the percentage of stained cells was evaluated by visual inspection, with the total cell number in the visual field counted as 100%.

In the tumor-transplanted NSG mice group, CD3-positive CAR-expressing T cell count in the peripheral blood reached the first peak level on Day 2, decreased up to Day 8, then reached the second peak on Day 11, followed by a decrease up to Day 29 (Figure 1). CD3-positive T cell count in the peripheral blood also showed a similar trend. The volume of the tumor tissue became undetectable on Day 18 (Figure 1). The applicant explained that the approximately 20-fold increase in the second peak from the first peak of CD3-positive CAR-expressing T cells in the peripheral blood was due to the stimulation of Abecma proliferation in response to the recognition of BCMA-expressing tumor cells, and that the number of CD3-positive CAR-expressing T cells in the peripheral blood decreased with the shrinkage of the tumor volume.

The percentage[8)] of CD3-positive T cells in the tumor tissue increased over time, while percentage[8)] of BCMA-expressing cells in the tumor tissue decreased. The percentage[8)] of CD3-positive T cells in the lung, liver, spleen, kidney, and bone marrow showed a transient increase on Day 8 or 15 (50%-75%, 25%-50%, 50%-75%, 1%-5%, and 1%-5%, respectively, of the entire tissue).

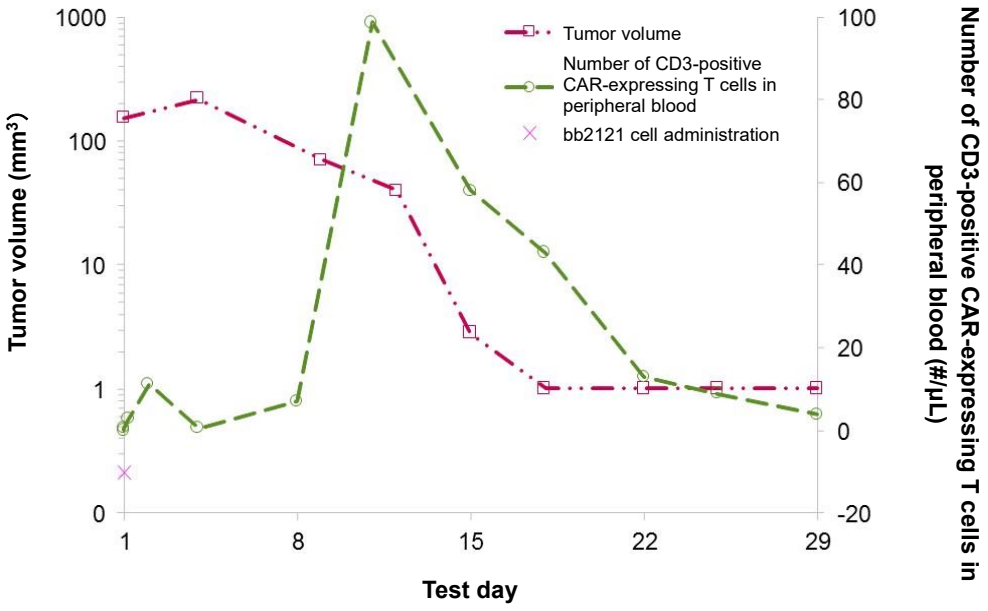


Figure 1. Changes over time in Abecma and tumor volume in NSG mice subcutaneously transplanted with human MM cell line

4.R Outline of the review conducted by PMDA

PMDA accepted the explanation of the applicant on the non-clinical biological disposition of Abecma, based on the submitted data.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to the non-clinical safety of Abecma: The results from pharmacological studies of Abecma in a mouse model of MM, gene insertion site analysis of the lentiviral vector, analysis of interleukin (IL)-2-dependent *in vitro* cell growth, and a study on the binding

of BCMA scFv using human cell membrane protein-expressing cells. The applicant also submitted data on the safety of impurities and excipients.

5.1 General toxicity

Since Abecma is a CAR-expressing T cell product manufactured from human T cells and acts specifically on human BCMA, safety information from conventional general toxicity studies is considered to be limited. Accordingly, general toxicity of Abecma was evaluated in *in vivo* pharmacological studies of Abecma in cancer-bearing animal models transplanted with human MM cell line.

5.1.1 Study in mouse model of MM treated with Abecma (CTD 4.2.1.1.4 and 4.2.1.1.5)

In studies administering a single intravenous dose of Abecma (maximum dose 1×10^7 cells) to NSG mice subcutaneously transplanted with human MM cell line (RPMI-8226 cells) [see Sections 3.2.1 and 3.2.2], viability, clinical signs, and body weight were evaluated. No toxicity attributable to Abecma was detected.

5.2 Evaluation of the possibilities of tumorigenesis and malignant transformation

In order to evaluate the possibility of malignant transformation of Abecma associated with the integration of lentiviral vector into chromosomes, gene insertion site analysis of lentiviral vector and *in vitro* analysis of IL-2-dependent cell growth of Abecma were conducted.

5.2.1 Gene insertion site analysis of lentiviral vector (CTD 4.2.3.3.1.1[9])

The gene insertion site of lentiviral vector was confirmed by deep sequencing (Table 13). The applicant explained that the results did not suggest any risk of malignant transformation of Abecma caused by the gene insertion.

Table 13. Gene insertion site analysis of lentiviral vector

Test system and study method	Results
The gene insertion site was identified by the analysis, by deep sequencing, of genomic DNA extracted from Abecma. The sequence of the insertion site was identified by Shearing-Extension Primer Tag Selection/Ligation-Mediated PCR.	• Extensive polyclonality was observed at the gene insertion site. • The same insertion pattern as that of wild-type lentivirus (CpG islands, highly DNase I-sensitive sites, and insertion into high GC content region) was observed. • Selective insertion of genes with potential oncogenicity (such as proto-oncogenes) into the transcription start region was not observed.

5.2.2 *In vitro* analysis of IL-2-dependent cell growth (CTD 4.2.3.4.3.1[9])

An *in vitro* growth study on Abecma cultured in the presence or absence of IL-2 (Table 14) did not show IL-2-independent cell growth, suggesting no evidence of malignant transformation of Abecma.

Table 14. *In vitro* analysis of IL-2-dependent cell growth of Abecma

Test system and study method	Results
Abecma was cultured in the presence or absence of IL-2, and cell count, etc., was evaluated up to Day 30.	In the presence of IL-2, Abecma showed a tendency of growth. In the absence of IL-2, in contrast, the cell count decreased over time and cells were undetectable on Day 22 of culture.

[9] Submitted as reference data.

5.3 BCMA scFv binding study using human cell membrane protein-expressing cells (CTD 4.2.3.7.7.3[9])

Using human embryonic kidney 293 (HEK 293 cells), each expressing either of 6,232 types of human cell membrane proteins, secretory proteins immobilized to cell surface, or heterodimers of human cell membrane proteins, binding with Abecma was investigated. Abecma was found to bind to 17 types of proteins including BCMA and to heterodimers. However, since the binding to 16 types of proteins other than BCMA was observed in the control group (cells not introduced with anti-BCMA CAR gene) as well. Accordingly, the applicant explained that Abecma binds specifically to BCMA.

5.4 Safety evaluation of impurities

Process-related impurities potentially remaining in the final product include residual viral vector, [redacted] protein, host cell DNA (gDNA), host cell protein, plasmid DNA, Impurity C, Impurity B, Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, and Impurity L.

Taking account of the residual amounts of these impurities in the clinical dose of Abecma, the applicant evaluated the safety of these impurities based on the clinical use experience, physiological concentrations, etc., and considered that these impurities would not pose a safety risk to humans.

5.5 Safety evaluation of excipients

The excipients of Abecma are composite electrolyte solution (Plasma-Lyte A) and cryopreserving solution (CryoStor CS10). The applicant conducted the safety evaluation of these excipients based on their content levels in Abecma at the clinical dose and considered that they would raise no safety concerns.

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and the following investigations, PMDA has concluded that Abecma raises no particular concerns about the non-clinical safety.

5.R.1 Reproductive and developmental toxicity

PMDA asked the applicant to explain the effect of Abecma on fetuses and neonates in pregnant women treated with Abecma and in women who became pregnant after treatment with Abecma.

The applicant's explanation:

Maternal T cells are detected in offspring (*Lab Invest.* 2006;86:1185-92), suggesting a possibility that CAR-expressing T cells in Abecma pass through the placenta into fetal blood and causes plasma insufficiency in plasma cells and hypogammaglobulinemia in the offspring, in theory. However, the absolute number of CAR-expressing T cells transferred into fetus via the placenta is considered to be minimal, causing only an extremely low risk of BCMA-positive cells depletion in developing fetuses. On the other hand, cyclophosphamide hydrate (cyclophosphamide) and fludarabine phosphate (fludarabine) used in lymphodepleting chemotherapy (LD chemotherapy) before Abecma infusion are known to have a risk of developmental toxicities such as congenital anomaly in fetuses. Given these, women of childbearing potential will be advised in the package insert to take contraceptive measures for a certain period of time during and after treatment with Abecma. The end date of the survey for the

most update report on the clinical safety of Abecma (data cutoff on [redacted], 20[redacted]) did not report any case of pregnancy after Abecma infusion or the administration of Abecma during pregnancy.

PMDA accepted the explanation of the applicant. However, information on reproductive and developmental toxicity of Abecma is extremely limited at present, and thus data related to the effects on the fetus should be collected in the post-marketing setting from pregnant women administered with Abecma, when such a case is once identified.

6. Clinical Biological Disposition and Outline of the Review Conducted by PMDA

The clinical biological disposition of Abecma was investigated based on the information obtained from Study CRB-401 and Study MM-001.

6.1 Study CRB-401 (CTD 5.3.5.2.2)

Changes over time in the level of Abecma-derived gene in blood were investigated in 62 subjects (21 in Part A, 41 in Part B) in Study CRB-401. In this study, a single dose of Abecma was administered intravenously at the target dose of 50×10^6, 150×10^6, 450×10^6, or 800×10^6 cells to patients with relapsed or refractory MM. The level of Abecma-derived gene in blood was measured by quantitative polymerase chain reaction (qPCR) using blood samples collected at baseline and on Days 2, 4, 7, 9, 11, 14, and 21 and Months 1, 2, 3, 6, 12, 18, and 24.

Following the administration of Abecma, the level of Abecma-derived gene in the blood increased rapidly, reaching the maximum level on Day 7 (median) in the 50×10^6 target dose group and Day 11 (median) in the 150×10^6 to 800×10^6 target dose groups, then decreased in a biphasic pattern (Figure 2). Table 15 shows the pharmacokinetic parameters of Abecma based on the level of Abecma-derived gene in each target dose group. The exposure (C_{max}, $AUC_{0\text{-}28days}$, $AUC_{0\text{-}3M}$, $AUC_{0\text{-}6M}$, and $AUC_{0\text{-}9M}$) increased with the increase in dose. The pharmacokinetic parameters varied widely between individual subjects, with the distribution of the exposure to Abecma overlapping throughout the entire target doses.

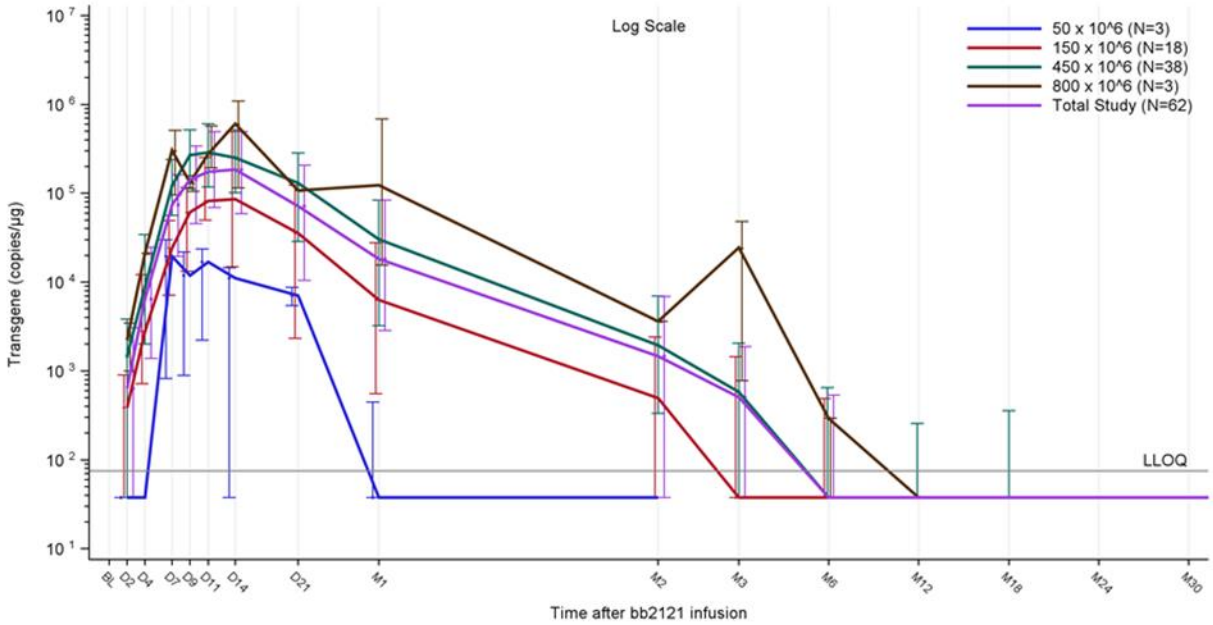


Figure 2. Changes over time in the level of Abecma-derived gene by target dose in Study CRB-401

Table 15. Pharmacokinetic parameters of Abecma-derived gene by target dose in Study CRB-401

Pharmacokinetic parameters	Target Abecma dose (in CAR-expressing T cell count)			
	50×10^6 N = 3	150×10^6 N = 18	450×10^6 N = 38	800×10^6 N = 3
C_{max}*1 (copies/µg)	10,907 (245)	107,335 (489)	306,727 (133)	389,278 (114)
T_{max}*2 (days)	7 (7-10)	11 (4-22)	11 (7-20)	11 (10-14)
T_{last}*2 (days)	21 (10-30)	29.5 (14-344)	91 (14-555)	175 (90-178)
$AUC_{0\text{-}28days}$*1 (day•copies/µg)	82,184 (722)	1,141,448 (509)	3,483,374 (155)	5,166,140 (184)
$AUC_{0\text{-}3M}$*1 (day•copies/µg)	288,445 (n = 1)	1,960,965 (468) (n = 16)	4,264,100 (171) (n = 36)	7,205,195 (262)
$AUC_{0\text{-}6M}$*1 (day•copies/µg)	288,445 (n = 1)	2,614,645 (432) (n = 13)	4,433,749 (179) (n = 35)	7,432,030 (272)
$AUC_{0\text{-}9M}$*1 (day•copies/µg)	288,445 (n = 1)	2,628,137 (433) (n = 13)	4,465,385 (179) (n = 35)	7,461,621 (270)

*1 Geometrical mean (coefficient of variation [CV] [%]) (individual value for n = 1)
*2 Median (range)

6.2 Study MM-001 (CTD 5.3.5.2.1)

Changes over time in the level of Abecma-derived gene in blood were investigated in 136 subjects (127 non-Japanese subjects, 9 Japanese subjects) in Study MM-001. In this study, a single dose of Abecma was administered intravenously at the target dose of 150×10^6, 300×10^6, or 450×10^6 cells to patients with relapsed or refractory MM. The level of Abecma-derived gene in blood was measured by qPCR using blood samples collected at baseline and on Days 2, 4, 7, 9, 11, 14, and 21 and Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24.

Following the administration of Abecma, the level of Abecma-derived gene in the blood increased rapidly, reaching the maximum level on Day 14 (median) in the 150×10^6 target dose group and Day 11 (median) in the 300×10^6 and 450×10^6 target dose groups, then decreased in a biphasic pattern (Figure 3). Table 16 shows the pharmacokinetic parameters of Abecma based on the level of Abecma-derived

gene in each target dose group. The exposure (C_{max}, $AUC_{0\text{-}28days}$, $AUC_{0\text{-}3M}$, $AUC_{0\text{-}6M}$, and $AUC_{0\text{-}9M}$) increased with the increase in dose. The pharmacokinetic parameters varied widely between individual subjects, with the distribution of the exposure to Abecma overlapping throughout the entire target doses.

The similarity of the biological distribution after administration of Abecma between Japanese and non-Japanese patients was discussed based on the pharmacokinetic parameters in Table 16. The applicant explained that the pharmacokinetic parameters in Japanese patients receiving a target dose of 450×10^6 cells were approximately 60% to 70% of those in non-Japanese patients receiving the same dose of Abecma, but the coefficient of variation (CV) of all parameter values exceeded 100%, suggesting that the biological disposition is similar between the two populations, considering inter-individual variability.

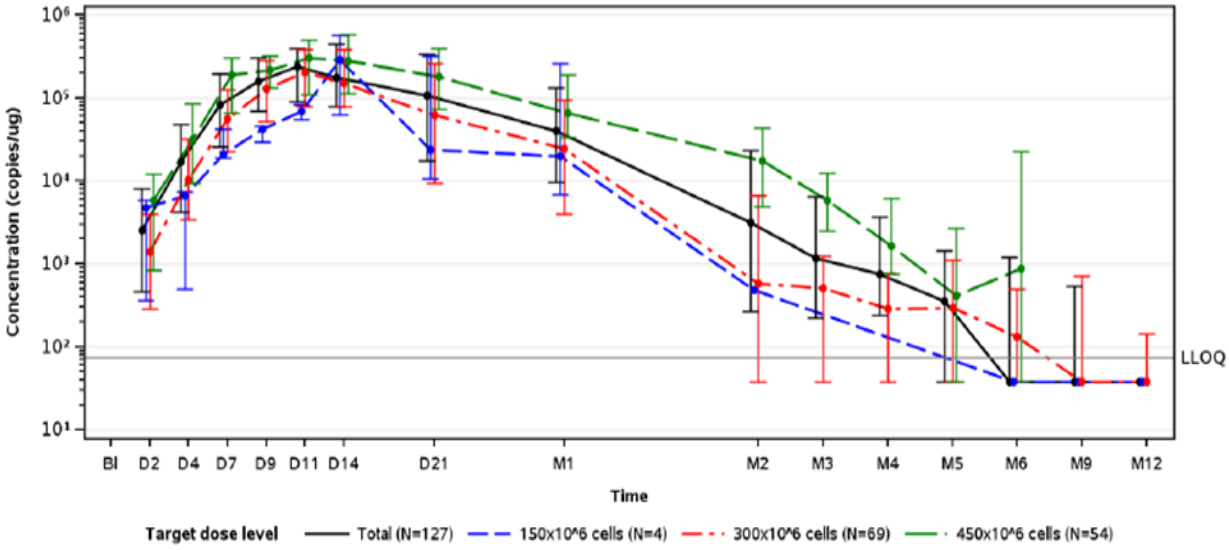


Figure 3. Changes over time in the level of Abecma-derived gene by target dose in Study MM-001

Table 16. Pharmacokinetic parameters of Abecma-derived gene by target dose in Study MM-001

Pharmacokinetic parameters	Target Abecma dose (in CAR-expressing T cell count)			
	Non-Japanese subjects			Japanese subjects
	150×10^6 cells N = 4	300×10^6 cells N = 69	450×10^6 cells N = 54	450×10^6 cells N = 9
C_{max}*1 (copies/µg)	204,229 (169)	180,185 (210)	321,117 (126)	212,672 (139)
T_{max}*2 (days)	14 (11-14)	11 (7-30)	11 (7-28)	11 (7-14)
T_{last}*2 (days)	58 (29-142)	119 (21-365)	115 (22-184)	92 (28-183)
$AUC_{0\text{-}28days}$*1 (day•copies/µg)	1,942,929 (154)	2,138,414 (215) (n = 68)	4,277,327 (152) (n = 53)	2,629,818 (174)
$AUC_{0\text{-}3M}$*1 (day•copies/µg)	4,372,535 (1,023) (n = 2)	2,952,312 (213) (n = 62)	5,955,266 (170) (n = 51)	3,636,213 (259)
$AUC_{0\text{-}6M}$*1 (day•copies/µg)	4,413,811 (997) (n = 2)	3,249,486 (214) (n = 59)	6,528,331 (180) (n = 47)	3,863,743 (288)
$AUC_{0\text{-}9M}$*1 (day•copies/µg)	4,420,074 (993) (n = 2)	3,276,494 (225) (n = 56)	6,572,367 (181) (n = 47)	3,910,822 (294)

*1 Geometric mean (CV [%])
*2 Median (range)

The relationship between the biological disposition of Abecma and its efficacy was investigated by measuring $AUC_{0\text{-}28days}$. As for the overall response rate, median $AUC_{0\text{-}28days}$ was 4,626,382 day•copies/µg

in patients with response (93 of 125 patients) and 845,455 day•copies/μg in patients without response (32 of 125 patients), being 5.47-fold higher in patients with response than patients without response. The median $AUC_{0\text{-}28days}$ for other efficacy endpoints was higher in patients with response as follows:

(1) 1,855,855 day•copies/μg in patients with less than very good partial response (VGPR) (58 of 125 patients) vs. 5,087,097 day•copies/μg in patients with VGPR or better (67 of 125 patients), being 2.74-fold higher in the latter group than in the former group.

(2) 2,810,607 day•copies/μg in patients with less than complete response (CR) (84 of 125 patients) vs. 5,231,339 day•copies/μg in patients with CR or better (41 of 125 patients), being 1.86-fold higher in the latter group than in the former group.

In addition to the above, evaluation of progression free survival (PFS) in patients classified according to $AUC_{0\text{-}28days}$ quartiles showed that (1) the lower the $AUC_{0\text{-}28days}$, the shorter the PFS; and (2) median PFS was 3 months in patients with the first quartile of $AUC_{0\text{-}28days}$ and ≥8 months with the second or higher quartile of $AUC_{0\text{-}28days}$. On the basis of the above, the applicant explained that the overall response rate, rate of VGPR or better, rate of CR or better, and PFS are correlated with the exposure to Abecma.

The relationship between the biological disposition of Abecma and its safety was investigated by measuring $AUC_{0\text{-}28days}$. The median C_{max} and $AUC_{0\text{-}28\ days}$ were 328,438 copies/μg and 4,452,614 day•copies/μg, respectively, in patients with cytokine release syndrome (CRS) receiving tocilizumab (genetical recombination) and 232,703 copies/μg and 2,740,635 day•copies/μg, respectively, in patients with CRS not receiving tocilizumab or patients without CRS, being 1.41-fold and 1.62-fold higher, respectively, in patients with CRS receiving tocilizumab. Similarly, the median C_{max} and $AUC_{0\text{-}28\ days}$ were 461,994 copies/μg and 6,786,554 day•copies/μg, respectively, in patients with CRS receiving corticosteroid and 271,435 copies/μg and 3,061,572 day•copies/μg, respectively, in patients with CRS not receiving corticosteroid or patients without CRS, being 1.70-fold and 2.22-fold higher, respectively, in patients with CRS receiving corticosteroid. In contrast, neurologic toxicity[10)] and neutropenia specified by the investigator showed no correlation with the exposure to Abecma. Based on the above, the applicant explained that there is a correlation between CRS necessitating tocilizumab or corticosteroid and exposure to Abecma.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the applicant's explanation about the clinical biological disposition of Abecma is acceptable.

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

The applicant submitted evaluation data on the efficacy and safety from 1 foreign phase I study and 1 global phase II study (Table 17).

[10)] Events determined as neurotoxicity related to CAR-expressing T cells by the investigator.

Table 17. List of clinical studies for efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	CRB-401	I	Part A Patients with relapsed or refractory MM Part B: Patients with relapsed or refractory MM	Part A: 24 Part B: 43	Intravenous administration of anti-BCMA CAR-expressing T cells at the following dose: Part A: A single dose of 50×10^6, 150×10^6, 450×10^6, or 800×10^6 cells Part B: A single dose of 150×10^6 or 450×10^6 cells In both parts, retreatment was allowed if the best response was SD or better and PD was observed ≥8 weeks after administration.	Efficacy Safety
	Global	MM-001	II	Patients with relapsed or refractory MM	149	A single intravenous administration of anti-BCMA CAR-expressing T cells at a dose of 150×10^6, 300×10^6, or 450×10^6 cells Retreatment was allowed if the best response was SD or better and PD was observed ≥8 weeks after administration.	Efficacy Safety

Each clinical study is summarized below. The main adverse events excluding deaths observed in each clinical study are presented in Section "9. Adverse Events Observed in Clinical Studies."

7.1 Evaluation data

7.1.1 Foreign clinical study

7.1.1.1 Foreign phase I study (CTD 5.3.5.2.2, Study CRB-401, ongoing since January 2016 [data cutoff on April 7, 2020])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of Abecma in patients with relapsed or refractory MM (target sample size, maximum 30 in Part A, 20-40 in Part B) at 9 study sites in the US. Table 18 shows the main inclusion/exclusion criteria.

Table 18. Main inclusion/exclusion criteria

Inclusion criteria
- Patients with relapsed or refractory MM who have had either of the following prior treatments:
  - Part A: Patients who have received ≥3 prior treatment regimens including immunomodulatory agent and proteasome inhibitor or who are refractory to both an immunomodulatory agent and a proteasome inhibitor (PD on or within 60 days of treatment with these agents)
  - Part B: Patients with previous exposure to immunomodulatory agent, proteasome inhibitors, and daratumumab, and are refractory to their last line of therapy
- Patients who have measurable disease, including ≥1 of the criteria below:
  - Serum M-protein ≥0.5 g/dL
  - Urine M-protein ≥200 mg/24 h
  - Serum free light chain (FLC) assay ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal
- Patients whose BCMA expression level in formalin-fixed paraffin-embedded specimens (obtained by bone marrow biopsies or plasmacytoma) meet the following criteria[*1]:
  - Part A: BCMA expression level ≥50%
  - Part B
    - ✓ Cohort 1: BCMA expression level <50%
    - ✓ Cohort 2: BCMA expression level ≥50%
    - ✓ Cohort 3: No requirement for BCMA expression level
- Patients with ECOG PS score of 0 or 1

Exclusion criteria
- Patients with previous history of an allogeneic hematopoietic stem cell transplantation or treatment with any gene therapy-based therapeutic for cancer
- Patients with past or current clinically significant central nervous system (CNS) disease[*2]

*1 In the clinical study protocol ver. 5.0, the requirements for BCMA expression level in cohorts 1 and 2 of Part B were amended, and cohort 3 not requiring BCMA pre-screening was added. In the previous version, 10 each of patients with BCMA expression level of ≥50% and <50% were to be enrolled.

*2 In the clinical study protocol ver. 4.1, exclusion criteria were amended to conform to those of Study MM-001. In the previous version, patients with a history of central nervous system disease had not been excluded.

The study consisted of 2 parts with the following objective, respectively:
- Part A (dose escalation phase): To determine the maximum tolerated dose (MTD) and a recommended Phase 2 dose (RP2D) (target dose) of Abecma in patients with tumors of a high BCMA expression rate (BCMA expression rate in plasma cells in bone marrow, ≥50%).
- Part B (dose expansion phase): To confirm the safety and efficacy of the target dose determined in part A.

Part B comprises 3 cohorts. Cohort 1 enrolled mainly patients with low BCMA expression rate (BCMA expression rate in bone marrow plasma cells, <50%), Cohort 2 enrolled patients with high BCMA expression rate (BCMA expression rate in bone marrow plasma cells, ≥50%), and Cohort 3 enrolled patients regardless of BCMA expression rate.

In Part A, a single dose of anti-BCMA CAR-expressing T cells was administered intravenously at the target dose of 50×10^6, 150×10^6, 450×10^6, or 800×10^6 cells. In Part B, a single dose of anti-BCMA CAR-expressing T cells was administered intravenously at the target dose of 150×10^6 or 450×10^6 cells. The actual dose was allowed to deviate from the target dose by up to ±20%. In patients who showed the best response of stable disease (SD) or better, Abecma could be administered again at the target dose of 150×10^6 or 450×10^6 anti-BCMA CAR-expressing T cells if PD was observed after Week 8. Patients who experienced a dose-limiting toxicity (DLT) were not eligible for retreatment.

In order to facilitate the engraftment and growth of Abecma in the body, Abecma infusion was preceded by treatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 over 30 minutes once daily for 3 consecutive days, starting from 5

days before administration of Abecma. While Abecma was in the process of manufacture, the patient was allowed to receive a bridging therapy for disease control. In Cohort 3 of Part B, medications and myeloma therapies to which the subject had not been previously exposed should not be used as bridging therapy. The bridging therapy was required to be completed ≥14 days before the start of LD chemotherapy.

All of 24 patients enrolled in Part A received leukapheresis, of whom 3 patients discontinued the study (adverse events, physician decision, and withdrawal by subject, 1 patient each), and the remaining 21 patients received LD chemotherapy and Abecma and were included in the DLT evaluation population. Of these, 8 patients received retreatment with Abecma. Study discontinuation occurred in 18 patients for reasons below: progressive disease in 15 patients (3 in the 50×10^6 cells group, 3 in the 150×10^6 cells group, 7 in the 450×10^6 cells group, and 2 in the 800×10^6 cells group); withdrawal by subject in 1 patient (the 150×10^6 cells group); death in 1 patient (the 450×10^6 cells group); and others in 1 patient (the 150×10^6 cells group).

In Part A, no DLT was observed up to Day 21 (duration of DLT evaluation), with no MTD identified. Based on the overall benefit-risk evaluation on the safety and efficacy results in Part A, RP2D of Abecma was determined to be 150×10^6 to 450×10^6 anti-BCMA CAR-expressing T cells by the safety evaluation committee.

All of 43 patients enrolled in Part B received leukapheresis, of whom 2 patients discontinued the study (physician decision and progressive disease, 1 patient each), and the remaining 41 patients received LD chemotherapy and Abecma. Of these, 10 patients received retreatment with Abecma. Study discontinuation occurred in 33 patients for reasons below: progressive disease in 23 patients (1 in the 150×10^6 cells group of Cohort 1, 7 in the 450×10^6 cells group of Cohort 1, 5 in the 150×10^6 cells group of Cohort 2, and 10 in the 450×10^6 cells group of Cohort 3); withdrawal by subject in 5 patients (1 in the 150×10^6 cells group in Cohort 1, 2 in the 150×10^6 cells group in Cohort 2, 2 in the 450×10^6 cells group in Cohort 3); and death in 5 patients (1 in the 450×10^6 cells group in Cohort 1, 2 in the 150×10^6 cells group in Cohort 2, 2 in the 450×10^6 cells group in Cohort 3). A total of 41 patients receiving Abecma were included in the primary safety and efficacy analysis set.

Table 19 shows the percentage of patients with the best response of partial response (PR) or better ("overall response rate") according to the independent response committee (IRC) assessment based on the criteria established by International Myeloma Working Group (IMWG) (IMWG Criteria) (*Lancet Oncol.* 2016;17:e328-46) at the data cutoff on April 7, 2020 when ≥15 months had passed after administration of Abecma to the last patient.

Table 19. Best response according to the IMWG criteria (IRC assessment, Abecma population, data cutoff on April 7, 2020)

	Number of patients (%)					
	50×10^6 cells N = 3	150×10^6 cells N = 18	450×10^6 cells N = 38	800×10^6 cells N = 3	150×10^6-450×10^6 cells N = 56	Total N = 62
sCR	0	6 (33.3)	15 (39.5)	2 (66.7)	21 (37.5)	23 (37.1)
CR	0	0	0	0	0	0
VGPR	0	1 (5.6)	11 (28.9)	1 (33.3)	12 (21.4)	13 (21.0)
PR	1 (33.3)	3 (16.7)	6 (15.8)	0	9 (16.1)	10 (16.1)
MR	0	1 (5.6)	1 (2.6)	0	2 (3.6)	2 (3.2)
SD	2 (66.7)	4 (22.2)	3 (7.9)	0	7 (12.5)	9 (14.5)
PD	0	3 (16.7)	2 (5.3)	0	5 (8.9)	5 (8.1)
NE	0	0	0	0	0	0
Response (sCR, CR, VGPR, or PR)	1	10	32	3	42	46
Overall response rate (%)	33.3	55.6	84.2	100	75.0	74.2
[95% CI*] (%)	[0.8, 90.6]	[30.8, 78.5]	[68.7, 94.0]	[29.2, 100]	[61.6, 85.6]	[61.5, 84.5]

* Clopper-Pearson method

As for safety (data cutoff on April 7, 2020), death occurred in 22 of 62 patients following Abecma administration (3 in the 50×10^6 cells group, 7 in the 150×10^6 cells group, 10 in the 450×10^6 cells group, 2 in the 800×10^6 cells group). The causes of death were disease progression in 17 patients (3 in the 50×10^6 cells group, 5 in the 150×10^6 cells group, 8 in the 450×10^6 cells group, 1 in the 800×10^6 cells group), adverse events in 5 patients (death and fungal infection in 1 patient each in the 150×10^6 cells group, multiple organ failure and cardio-respiratory arrest in 1 patient each in the 450×10^6 cells group, mucormycosis in 1 patient in the 800×10^6 cells group). Among the deaths caused by adverse events, the death in 1 patient[11)] in the 150×10^6 cells group occurred within 8 weeks after the initial dose of Abecma, and its causal relationship to Abecma could not be ruled out.

7.1.2 Global study

7.1.2.1 Global phase II study (CTD 5.3.5.2.1, Study MM-001, ongoing since [redacted] 20[redacted] [data cutoff on December 21, 2020])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of Abecma in patients with relapsed or refractory MM (target sample size, 150 patients [140 in non-Japanese cohort, 10 in Japanese cohort]) at 24 study sites (4 Japanese sites) in 8 countries including Japan. Table 20 shows the main inclusion/exclusion criteria.

11) A 6[redacted]-year-old male with a prior treatment with 9 regimens of chemotherapy. On Day 1 (the day of Abecma administration), the patient had Grade 2 CRS, Grade 3 febrile neutropenia, Grade 4 thrombocytopenia, and Grade 3 haemoglobin decreased. CRS resolved on Day 4 but neutropenia remained Grade 4. On Day 8, Grade 2 CRS occurred again, accompanied by hypotension, pyrexia, hepatic dysfunction (transaminase increased, bilirubin increased), etc. After prophylactic administration of corticosteroid and treatment with tocilizumab, CRS resolved on Day 12 but hepatic dysfunction and decreased hypocytosis persisted. On Day 51, death was reported but the cause of death was unknown because pathological anatomy was not performed due to the refusal of the subject's family. The death was assessed by the investigator to be causally related to Abecma.

Table 20. Main inclusion/exclusion criteria

Inclusion criteria:
- Patients with relapsed or refractory MM who have had the following prior treatments:
  - Patients who have received ≥3 prior MM treatment regimens (Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen.)
  - Patients who have undergone ≥2 consecutive cycles of treatment for each regimen, unless PD was the best response to the regimen.
  - Patients with previous exposure to immunomodulatory agent, proteasome inhibitors, and anti-CD38 antibody
  - Refractory to their last line of therapy (Refractory is defined as documented PD during or within 60 days of completing treatment)
- Patients who have measurable disease, including ≥1 of the criteria below:
  - Serum M-protein ≥1.0 g/dL
  - Urine M-protein ≥200 mg/24 h
  - Serum FLC assay ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal
- Patients with ECOG PS score of 0 or 1

Exclusion criteria
- Patients with previous history of an allogeneic hematopoietic stem cell transplantation or treatment with any gene therapy-based therapeutic for cancer or cellular therapy for cancer or BCMA targeted therapy
- Patients with known CNS involvement with myeloma
- Patients with past or current clinically significant CNS disease

The study consisted of a pre-treatment phase (period from leukapheresis to LD chemotherapy and Abecma manufacturing period after screening), a treatment phase (from the start of LD chemotherapy to Abecma administration), and a post-treatment follow-up phase (≥24 months after Abecma administration or for up to 5 years until documented PD, whichever is longer).

In the non-Japanese patient group, a single dose of anti-BCMA CAR-expressing T cells was administered intravenously at the target dose of 150×10^6, 300×10^6, and 450×10^6 cells.[12)] In the Japanese patient cohort, the target dose of 450×10^6 cells was administered intravenously as a single dose in all patients. In patients with the best response of SD or better, patients were allowed to receive a retreatment with Abecma at the target dose of 150×10^6, 300×10^6, or 450×10^6 anti-BCMA CAR-expressing T cells if PD was observed after Week 8 and if cryopreserved Abecma was available for use.[13)]

In order to facilitate the engraftment and growth of Abecma in the body, Abecma infusion was preceded by treatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 over 30 minutes once daily for 3 consecutive days, starting from 5 days before Abecma. While Abecma was in the process of manufacture, the patient was allowed to receive a bridging therapy for disease control. Bridging therapies included corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. Medications and myeloma therapies to which the subject had not been previously exposed should not be used as bridging therapy. The bridging therapy was required to be completed ≥14 days before the start of LD chemotherapy.

At the start of the study, Abecma was to be administered at a dose of 150×10^6 cells or 300×10^6 cells. With the expected value of overall response rate, the primary efficacy endpoint, specified 70% with the threshold level of 50%, the number of subjects needed to ensure the statistical power of 96% at the one-

12) The upper limit of the actual dose permitted was 540×10^6 cells, which falls within the range of 450×10^6 cells +20%.
13) Repeat leukapheresis had been allowed in the clinical study protocol, up to version 1.0, and remanufacture from cryopreserved PBMC had been allowed up to version 3.0.

sided significance level of 2.5% was calculated to be 80. In accordance with this assumption, the target number of subjects in the non-Japanese cohort was determined to be 94, by allowing the dropout of 15%. After the start of the study, results of Study CRB-401 suggested a dose response across the dose range of 150×10^6 to 450×10^6 cells, whereupon the dose of 450×10^6 cells was added in the clinical study protocol, ver. 2.0 (dated [redacted], 20[redacted]) of this study. In the initial protocol, the target dose of 450×10^6 cells had been expected to be administered to approximately 15 subjects. In order to enroll a sufficient number of subjects in the group receiving the target dose of 450×10^6 cells, the target sample size of the non-Japanese cohort was changed to a maximum of 140. Of the 140 subjects to be enrolled, 119 subjects were expected to receive Abecma. Under this sample size, the statistical power was calculated to exceed 99%, assuming the expected overall response rate of 70% with threshold level of 50% and the one-sided significance level of 2.5%.

A total of 140 subjects were enrolled in the non-Japanese cohort and all of them received leukapheresis. The study was then discontinued before LD chemotherapy in 8 patients (adverse event in 1 patient, physician decision in 3 patients, progressive disease in 1 patient, failure to manufacture product in 1 patient,[14)] and withdrawal by subject in 2 patients) and after LD chemotherapy but before Abecma administration in 4 patients (death and withdrawal by subject in 2 patients each). A total of 128 patients receiving Abecma (4 in the 150×10^6 cells group, 70 in the 300×10^6 cells group, 54 in the 450×10^6 cells group) were included in the primary efficacy and safety analysis sets. In the Japanese cohort, 9 patients were enrolled and all of them received Abecma at a dose of 450×10^6 cells after leukapheresis. A total of 31 patients (2 in the 300×10^6 cells group, 29 in the 450×10^6 cells group; all of them were non-Japanese patients) underwent retreatment.

The primary endpoint of the study was the overall response rate assessed by IRC according to the IMWG criteria (*Lancet Oncol*. 2016;17:e328-46). Efficacy was to be evaluated based mainly on the results obtained in the non-Japanese cohort. Table 21 shows the results of the primary endpoint in the non-Japanese cohort at the data cutoff point of October 16, 2019, when ≥10 months had passed from administration of Abecma to the last non-Japanese patient. The overall response rate [95% confidence interval (CI)] (%) was 73.4 [65.8, 81.1], which was statistically significantly greater than the threshold level of 50%.[15)]

14) Apheresis was performed twice, and manufacture of Abecma was attempted twice, but the target cell growth was not achieved due to the poor quality of the apheresis product.

15) The null hypothesis (overall response rate ≤50%) was determined based on the observation that the total response rate to daratumumab was 29% to 36% in patients with relapsed or refractory MM with ≥3 lines of prior treatment including immunomodulatory agent and proteasome inhibitor, or resistant to both immunomodulatory agent and proteasome inhibitor (*Haematologica*. 2015;100:1327-33, *Blood*. 2014;123:1826-32, *Lancet Oncol*. 2013;14:1055-66).

Table 21. The best response according to the IMWG criteria (IRC assessment, efficacy analysis set, data cutoff on October 16, 2019)

	Number of patients (%)			
	Non-Japanese cohort			
	150×10^6 cells N = 4	300×10^6 cells N = 70	450×10^6 cells N = 54	150×10^6 to 450×10^6 cells N = 128
sCR	1 (25.0)	19 (27.1)	19 (35.2)	39 (30.5)
CR	0	1 (1.4)	0	1 (0.8)
VGPR	1 (25.0)	10 (14.3)	15 (27.8)	26 (20.3)
PR	0	18 (25.7)	10 (18.5)	28 (21.9)
MR	0	2 (2.9)	0	2 (1.6)
SD	1 (25.0)	14 (20.0)	7 (13.0)	22 (17.2)
PD	1 (25.0)	6 (8.6)	1 (1.9)	8 (6.3)
NE	0	0	2 (3.7)	2 (1.6)
Response (sCR, CR, VGPR, or PR)	2	48	44	94
Overall response rate (%)	50.0	68.6	81.5	73.4
[95% CI[*1]] (%)	[6.8, 93.2]	[56.4, 79.1]	[68.6, 90.7]	[65.8, 81.1]
P value (one-sided)[*2]				<0.0001

*1 Wald test for non-Japanese patients (150×10^6-450×10^6 cells), Clopper-Pearson test for others
*2 One-sided significance level of 2.5%, one sample binomial test with normal approximation for 50% threshold

Table 22 shows the efficacy results of this study, including those of the Japanese cohort, at the data cutoff on December 21, 2020, when ≥3 months had passed from administration of Abecma to the last Japanese patient. The overall response rate [95% CI] (%) in the Japanese cohort was 88.9 [51.8, 99.7].

Table 22. Best response according to the IMWG criteria (IRC assessment, efficacy analysis set, data cutoff on December 21, 2020)

	Number of patients (%)					
	Japanese cohort	Non-Japanese cohort				Entire population
	450×10^6 cells N = 9	150×10^6 cells N = 4	300×10^6 cells N = 70	450×10^6 cells N = 54	150×10^6-450×10^6 cells N = 128	N = 137
sCR	5 (55.6)	1 (25.0)	19 (27.1)	21 (38.9)	41 (32.0)	46 (33.6)
CR	0	0	1 (1.4)	0	1 (0.8)	1 (0.7)
VGPR	3 (33.3)	1 (25.0)	11 (15.7)	14 (25.9)	26 (20.3)	29 (21.2)
PR	0	0	17 (24.3)	9 (16.7)	26 (20.3)	26 (19.0)
MR	0	0	2 (2.9)	0	2 (1.6)	2 (1.5)
SD	1 (11.1)	1 (25.0)	14 (20.0)	7 (13.0)	22 (17.2)	23 (16.8)
PD	0	1 (25.0)	6 (8.6)	2 (3.7)	9 (7.0)	9 (6.6)
NE	0	0	0	1 (1.9)	1 (0.8)	1 (0.7)
Response (sCR, CR, VGPR, or PR)	8	2	48	44	94	102
Overall response rate (%) [95% CI[*]] (%)	88.9 [51.8, 99.7]	50.0 [6.8, 93.2]	68.6 [56.4, 79.1]	81.5 [68.6, 90.7]	73.4 [65.8, 81.1]	74.5 [67.1, 81.8]

* Wald test for non-Japanese patients (150×10^6-450×10^6 cells), Clopper-Pearson test for others

As for safety (data cutoff on December 21, 2020), death occurred in 65 patients after administration of Abecma. The causes of death were disease progression in 43 patients (2 in the 150×10^6 cells group, 28 in the 300×10^6 cells group, 13 in the 450×10^6 cells group), adverse events in 12 patients (CRS, pneumonia cytomegaloviral, sepsis, lung adenocarcinoma, and cerebral haemorrhage in 1 patient each in the 300×10^6 cells group; bronchopulmonary aspergillosis, gastrointestinal haemorrhage, respiratory tract infection, subdural haematoma, toxicity to various agents,[16)] septic shock, and cerebral haematoma

16) A 6[redacted]-year-old male. The patient was diagnosed with PD on Day 269 and started treatment with elotuzumab (genetical recombination), pomalidomide, and dexamethasone on Day 318, but discontinued the treatment due to toxicity (pyrexia). Subsequently, treatment was resumed with dexamethasone, cisplatin, cyclophosphamide, etoposide, and bortezomib (treatment start date is unknown), but death due to the toxicity of these drugs was reported on Day 388. A causal relationship of the death to Abecma was denied.

in 1 patient each in the 450 × 10^6 cells group), and others in 10 patients (death, unknown, euthanasia, and cardiac arrest in 1 patient each in the 300 × 10^6 cells group; and death and unknown in 2 patients each, and sepsis and plasma cell leukaemia in 1 patient each in the 450 × 10^6 cells group). Among them, 2 Japanese patients died after administration of Abecma. The cause of death was disease progression and death in 1 patient each. In 1 death, the patient withdrew the consent to participate in the follow-up study after administration of Abecma and died >8 weeks after administration of Abecma.

Among the deaths due to adverse events, the causal relationship to Abecma could not be ruled out in 2 patients in the 300 × 10^6 cells group (CRS[17)] and pneumonia cytomegaloviral[18)]) and in 2 patients in the 450 × 10^6 cells group (bronchopulmonary aspergillosis[19)] and gastrointestinal haemorrhage[20)]).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

As a result of the following review, PMDA has concluded that Abecma was shown to have a certain level of efficacy in patients with relapsed or refractory MM.

7.R.1.1 Efficacy endpoint

The applicant's explanation about the reason for using the overall response rate as the primary endpoint in Study MM-001:

The response means decreased tumor volume and disease control, providing an expectation for symptom improvement associated with reduced tumor volume and for prolonged PFS and overall survival (OS) associated with the delayed relapse (disease progression). Therefore, the overall response rate was used as the primary endpoint in Study MM-001.

PMDA's view:

The applicant's explanation is understandable. However, results of duration of response (DOR), PFS, and OS are also important in evaluating the treatment effect against relapsed or refractory MM. Accordingly, the efficacy of Abecma was evaluated based mainly on the overall response rate, with the results of DOR, PFS, and OS taken into account.

7.R.1.2 Results of efficacy evaluation

The applicant's explanation about the efficacy of Abecma in patients with relapsed or refractory MM:

In Study MM-001, overall response rate [95% CI] (%) in the non-Japanese cohort by IRC assessment according to the IMWG criteria, the primary efficacy endpoint, was 73.4 [65.8, 81.1] which exceeded

17) A 4[redacted]-year-old female with a prior treatment with 14 regimens of chemotherapy. On Day 2, Grade 3 CRS, Grade 2 encephalopathy, and Grade 4 cytopenia occurred. The patient underwent artificial respiration, treatment with tocilizumab and dexamethasone. On Day 4, CRS worsened to Grade 4 with haemophagocytic lymphohistiocytosis, hypotension, and multiple organ dysfunction syndrome. Despite multidisciplinary treatment, symptoms aggravated, and death was reported on Day 5.

18) A 5[redacted]-year-old male with a prior treatment with 7 regimens of chemotherapy. On Day 85, Grade 2 upper respiratory tract infection occurred, and the patient was hospitalized with a diagnosis of Grade 3 pneumonia cytomegaloviral on Day 98. The patient also experienced pneumocystis infection. Despite multidisciplinary treatments, symptoms did not improve, and death was reported on Day 113.

19) A 7[redacted]-year-old male with a prior treatment with 3 regimens of chemotherapy. Grade 1 CRS occurred on Day 1, which worsened to Grade 2 on Day 5 and to Grade 3 on Day 8. Grade 4 haemophagocytic lymphohistiocytosis occurred on Day 9, followed by Grade 4 bronchopulmonary aspergillosis on Day 29. Treatment with antifungal agents was given, but the patient experienced complications including enterococcal bacteraemia and cerebral embolism due to *Aspergillus* mass. Despite multidisciplinary treatments, symptoms did not improve, and death was reported on Day 55.

20) A 5[redacted]-year-old male with a prior treatment with 7 regimens of chemotherapy. On Day 1, Grade 1 CRS, Grade 4 febrile neutropenia, and Grade 4 thrombocytopenia occurred. On Day 3, CRS worsened to Grade 3, accompanied by Grade 3 neurotoxicity. Grade 4 sepsis occurred on Day 22, and gastrointestinal haemorrhage (from rectum) occurred on Day 36, and death was reported.

the pre-defined efficacy standard (50%) (data cutoff on October 16, 2019). Also, in the Japanese cohort, the overall response rate [95% CI] (%) was 88.9 [51.8, 99.7], which was not significantly different from the rate in the non-Japanese cohort (data cutoff on December 21, 2020).

The median DOR[21)] [95% CI] (months) in the entire population (102 patients) was 11.0 [9.9, 12.5] at the data cutoff on December 21, 2020. The median DOR [95% CI] (months) in the non-Japanese cohort receiving each target dose was 15.8 [2.8, 28.8] at 150 × 10^6 cells (2 patients), 9.9 [5.6, 11.0] at 300 × 10^6 cells (48 patients), and 11.3 [10.3, 16.9] at 450 × 10^6 cells (44 patients). Figure 4 shows the Kaplan-Meier curve for each target dose.

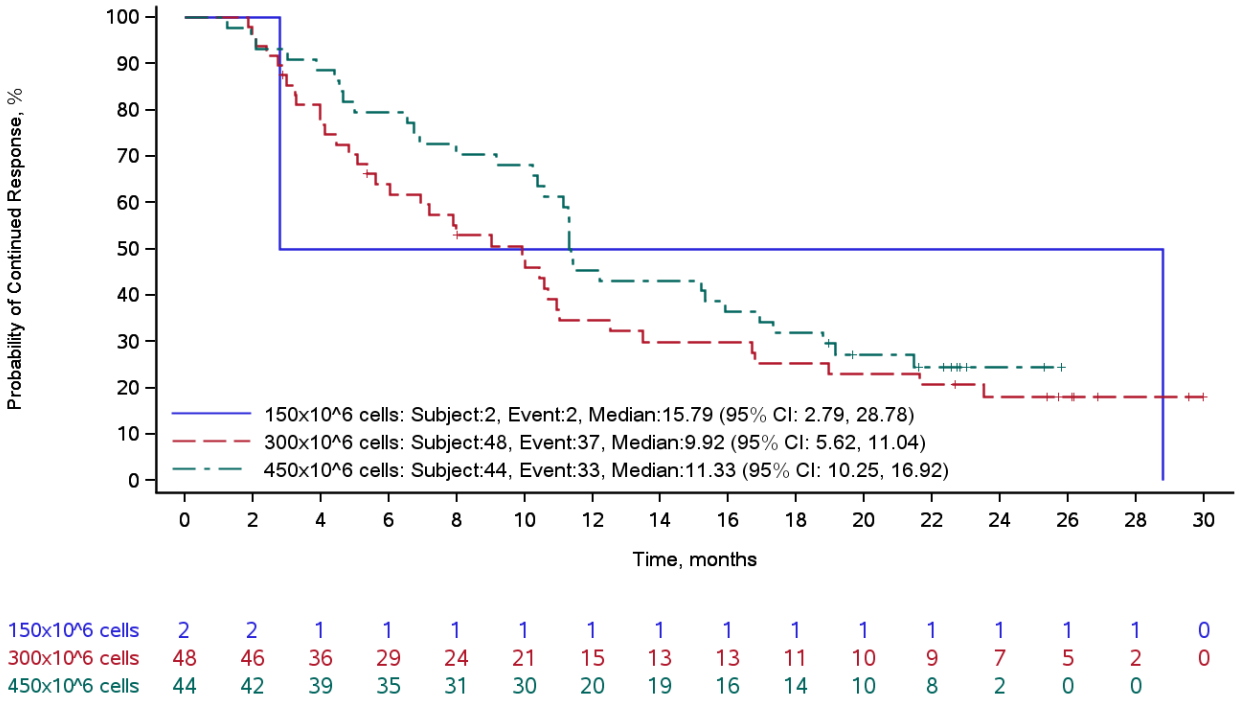


Figure 4. Kaplan-Meier curve of DOR for each target dose in the non-Japanese cohort of Study MM-001 (efficacy analysis set, data cutoff on December 21, 2020)

The median PFS [95% CI] (months) in the entire population (137 patients) was 8.9 [6.0, 11.9] at the data cutoff on December 21, 2020. The median PFS [95% CI] (months) in the non-Japanese cohort receiving each target dose was 2.8 [1.0, 29.7] at 150 × 10^6 cells (4 patients), 5.8 [4.2, 8.9] at 300 × 10^6 cells (70 patients), and 12.2 [8.6, 13.1] at 450 × 10^6 cells (54 patients). Figure 5 shows the Kaplan-Meier curve for each target dose.

[21)] Duration of response in patients with the best response of PR or better by IRC assessment according to the IMWG criteria

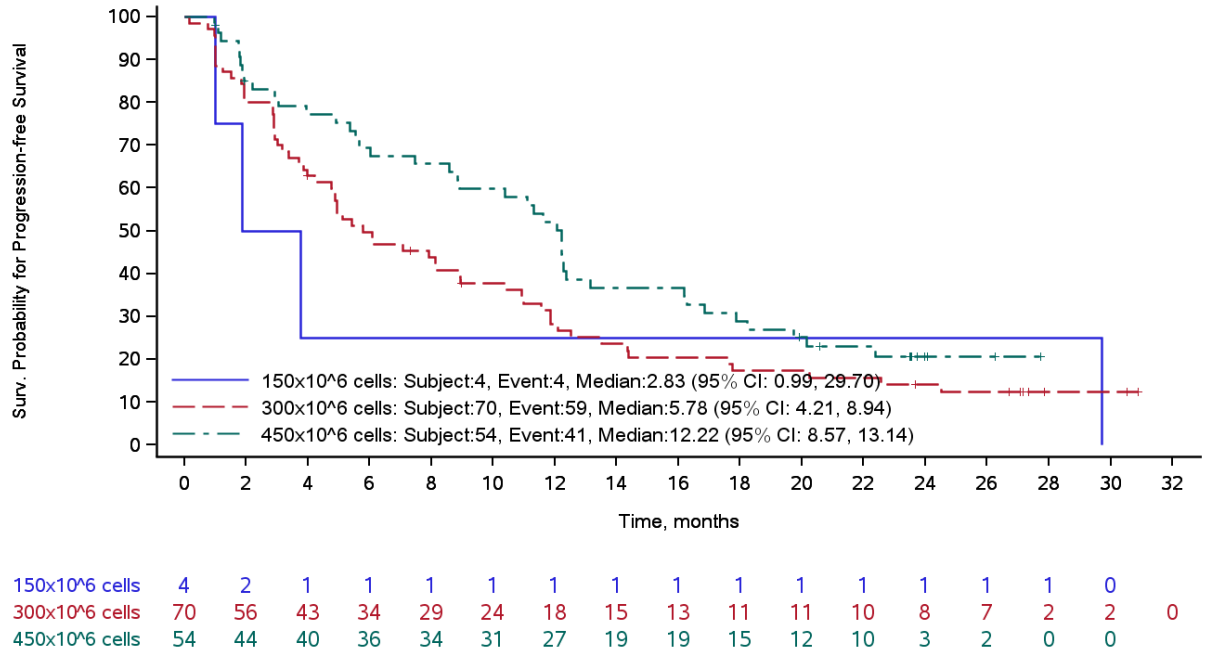
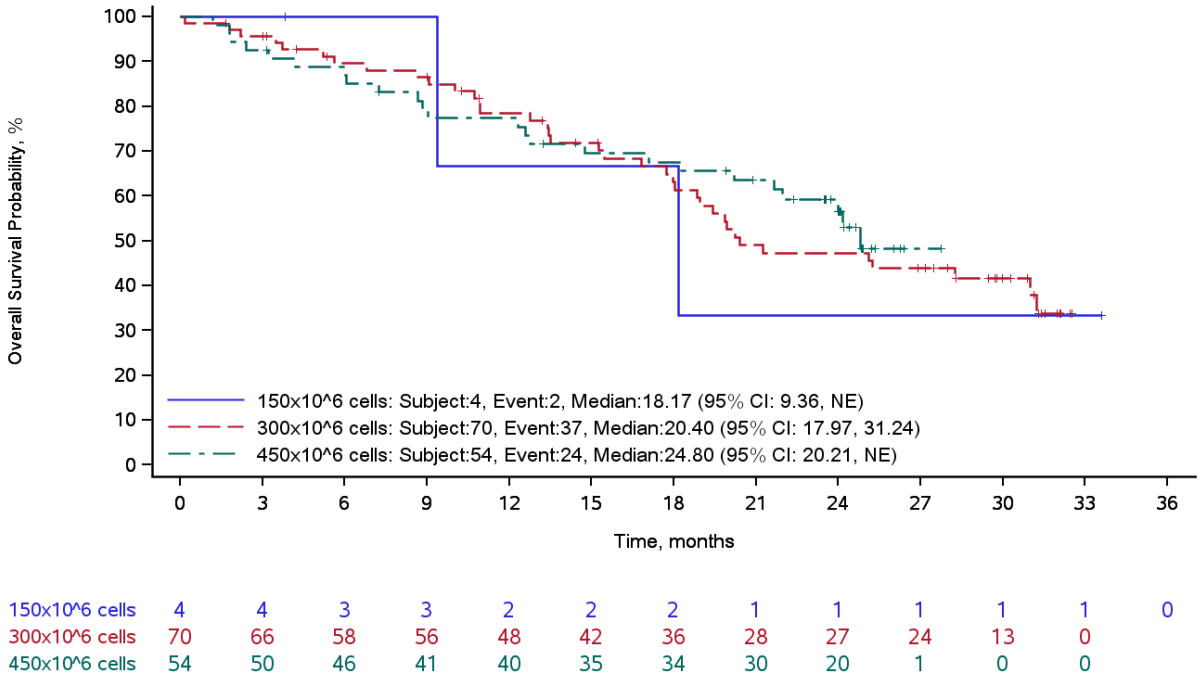


Figure 5. Kaplan-Meier curve of PFS at each target dose in the non-Japanese cohort of Study MM-001 (efficacy analysis set, data cutoff on December 21, 2020)

The median OS [95% CI] (months) in the entire population (137 patients) was 24.8 [19.9, 31.2] at the data cutoff on December 21, 2020. The median OS [95% CI] (months) in the non-Japanese cohort receiving each target dose was 18.2 [9.4, not estimable] at 150 × 10^6 cells (4 patients), 20.4 [18.0, 31.2] at 300 × 10^6 cells (70 patients), and 24.8 [20.2, not estimable] at 450 × 10^6 cells (54 patients). Figure 6 shows the Kaplan-Meier curve for each target dose.



NE: Not estimable

Figure 6. Kaplan-Meier curve of OS in the non-Japanese cohort receiving each target dose in Study MM-001 (efficacy analysis set, data cutoff on December 21, 2020)

Efficacy results in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6 cells in Study CRB-401 were as follows (data cutoff on April 7, 2020).

The overall response rate [95% CI] (%) was 75.0 [61.6, 85.6].

The median DOR[21] [95% CI] (months) was 10.3 [7.4, 13.6]. The median DOR [95% CI] (months) at each target dose was 10.8 [2.1, not estimable] at 150×10^6 cells (10 patients) and 10.0 [7.2, 14.8] at 450×10^6 cells (32 patients).

The median PFS [95% CI] (months) was 8.8 [5.9, 11.3]. The median PFS [95% CI] (months) at each target dose was 4.5 [2.0, 10.9] at 150×10^6 cells (18 patients) and 9.0 [7.2, 12.2] at 450×10^6 cells (38 patients).

The median OS [95% CI] (months) was 36.6 [23.2, not estimable]. The overall survival rate at Month 6, 12, 18, 24, 30, and 36 was 88.9%, 82.7%, 74.5%, 65.7%, 60.2%, and 50.2%, respectively. The median OS [95% CI] (months) at each target dose was not estimable [10.8, not estimable] at 150×10^6 cells and 34.2 [23.2, not estimable] at 450×10^6 cells.

The efficacy of Abecma was also evaluated based on the comparison with the external control, as shown below.

In Study NDS-MM-003[22] which collected the real world data, the overall response rate in 190 patients who met the enrollment criteria of Study MM-001 and received an available next treatment [eligible RRMM cohort] was 32.2%, the median DOR was 9.0 months, the median PFS was 3.5 months, and the median OS was 14.7 months (data cutoff on [redacted], 20[redacted]). According to the reports of clinical studies in patients with relapsed or refractory MM with a prior treatment with an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody (*Leukemia*. 2019;33:2266-75, *N Engl J Med*. 2019;381:727-38, *J Clin Oncol*. 2018;36:859-66, *Lancet Oncol.* 2020;21:207-21), the overall response rate was 26% to 34%, the median PFS was 2.9 to 4.9 months, and the median OS ranged from 5.6 to 9.3 months. The above results indicated that Studies MM-001 and CRB-401 suggested the efficacy of Abecma, although there are limits to the comparison with the external control.

In the Japanese cohort (target dose 450×10^6 cells) of Study MM-001, the overall response rate was 88.9% (55.6% achieved stringent complete response [sCR], 33.3% achieved VGPR), the median DOR [95% CI] (months) was not estimable [3.9, not estimable], the median PFS (months) [95% CI] was not estimable [4.9, not estimable], and the median OS (months) [95% CI] was not estimable [3.3, not estimable]. The overall survival rate at Month 3, 6, 9, 12, and 15 estimated by Kaplan-Meier method was 100%, 88.9%, 88.9%, 77.8%, and 77.8%, respectively. These results suggest efficacy of Abecma in Japanese patients.

[22] A non-interventional, retrospective foreign study to investigate the treatment patterns of relapsed or refractory MM under actual clinical use (patients after treatment with an immunomodulatory agent, a proteasome inhibitor, or an anti-CD38 antibody, in particular)

Although there are no data supporting the efficacy of Abecma in Japanese patients at 150×10^6 to 300×10^6 cells, the target dose range not investigated in the Japanese cohort, the applicant explained that Abecma is expected to be effective in Japanese patients within this dose range as well, for the following reasons:

- Efficacy of Abecma at the target dose of 450×10^6 cells is similar between Japanese and non-Japanese patients
- In the Japanese patients receiving the target dose of 450×10^6 cells, the pharmacokinetic parameters ($AUC_{0\text{-}28days}$ and C_{max}) were approximately 60% to 70% of those of non-Japanese patients. However, CV of all parameter values exceeded 100%, suggesting that the biological disposition is similar between the two populations, given the observed wide variations of data [see Section 6.2].
- The Japanese and foreign clinical practice guidelines are not significantly different in the pathology of relapsed or refractory MM or the diagnosis and treatment algorithm.

PMDA's view:
The above explanation of the applicant is understandable. Results of Studies MM-001 and CRB-401 demonstrated a certain level of efficacy of Abecma in patients with relapsed or refractory MM. The appropriateness of the dosage regimen of Abecma is discussed continuously in Section "7.R.4.2 Dosage and administration of Abecma."

7.R.2 Safety [for adverse events, see Section "9. Adverse Events Observed in Clinical Studies."]

As a result of the following reviews, PMDA concluded that adverse events requiring special attention in Abecma treatment are CRS, haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, cytopenia, hypersensitivity, hypogammaglobulinaemia, and tumor lysis syndrome (TLS). Caution should be exercised against these adverse events in the use of Abecma.

In addition, PMDA concluded that Abecma is tolerable, given appropriate measures i.e., monitoring and management of adverse events taken by a physician with sufficient knowledge and experience in the treatment of MM at a medical institution well-equipped for dealing with these adverse events.

7.R.2.1 Safety profile of Abecma and differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of Abecma:
Table 23 shows the summary of the safety in Study MM-001 (data cutoff on December 21, 2020).

Table 23. Summary of safety (Study MM-001, Abecma cohort, data cutoff on December 21, 2020).

	Number of patients (%)			
	150×10^6 cells N = 4	300×10^6 cells N = 70	450×10^6 cells N = 63	150×10^6-450×10^6 cells N = 137
All adverse events	4 (100)	70 (100)	63 (100)	137 (100)
Grade ≥3 adverse events	4 (100)	69 (98.6)	63 (100)	136 (99.3)
Serious adverse events	4 (100)	46 (65.7)	44 (69.8)	94 (68.6)
Death	2 (50.0)	37 (52.9)	26 (41.3)	65 (47.4)
Death due to adverse events	0	5 (7.1)	7 (11.1)	12 (8.8)

The incidence of serious adverse events in Study MM-001 was as described in Section "9.2 Global phase II study (Study MM-001)."

Table 24 shows the summary of safety in Study CRB-401 (data cut-off on April 7, 2020).

Table 24. Summary of safety (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

	Number of patients (%)					
	50×10^6 cells N = 3	150×10^6 cells N = 18	450×10^6 cells N = 38	800×10^6 cells N = 3	150×10^6-450×10^6 cells N = 56	50×10^6-800×10^6 cells N = 62
All adverse events	3 (100)	18 (100)	38 (100)	3 (100)	56 (100)	62 (100)
Grade ≥3 adverse events	3 (100)	18 (100)	37 (97.4)	3 (100)	55 (98.2)	61 (98.4)
Serious adverse events	3 (100)	13 (72.2)	29 (76.3)	3 (100)	42 (75.0)	48 (77.4)
Death due to adverse events	0	1 (5.6)	2 (5.3)	1 (33.3)	3 (5.4)	4 (6.5)

Serious adverse events observed in ≥2 patients at any of the target doses in Study CRB-401 were as shown in Section "9.1 Foreign phase I study (Study CRB-401)."

The applicant's explanation about the difference in the safety of Abecma between Japanese and non-Japanese patients:
Table 25 shows a summary of safety in the Japanese and non-Japanese cohorts in Study MM-001. Table 26 shows all-grade and Grade ≥3 adverse events with a ≥20% higher incidence in the Japanese cohort than in the non-Japanese cohort.

Table 25. Summary of safety (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

	Number of patients (%)			
	Japanese cohort	Non-Japanese cohort		Entire population
	450×10^6 cells N = 9	450×10^6 cells N = 54	150×10^6-450×10^6 cells N = 128	150×10^6-450×10^6 cells N = 137
All adverse events	9 (100)	54 (100)	128 (100)	137 (100)
Grade ≥3 adverse events	9 (100)	54 (100)	127 (99.2)	136 (99.3)
Serious adverse events	4 (44.4)	40 (74.1)	90 (70.3)	94 (68.6)
Adverse events leading to death	1 (11.1)	14 (25.9)	34 (26.6)	35 (25.5)
ICU admission	3 (33.3)	13 (24.1)	26 (20.3)	29 (21.2)
ICU admission due to adverse events	1 (11.1)	13 (24.1)	26 (20.3)	27 (19.7)

Table 26. Adverse events with a ≥20% higher incidence in Japanese cohort than in non-Japanese cohort (Study MM-001, target dose 450×10^6 cells, data cutoff on December 21, 2020)

PT (MedDRA/J ver.22.0)	Number of patients (%)	
	Japanese cohort N = 9	Non-Japanese cohort N = 54
Leukopenia	8 (88.9)	18 (33.3)
Lymphopenia	7 (77.8)	15 (27.8)
Hypophosphataemia	5 (55.6)	14 (25.9)
Hypogammaglobulinaemia	4 (44.4)	11 (20.4)
Pruritus	2 (22.2)	1 (1.9)
Grade ≥3 adverse events		
Leukopenia	8 (88.9)	18 (33.3)
Lymphopenia	7 (77.8)	14 (25.9)
Hypophosphataemia	5 (55.6)	8 (14.8)

The tendency of the occurrence of adverse events in Japanese patients was similar to that in the entire population. There was no significant safety problem unique to Japanese patients.

PMDA's view:
Serious adverse events were observed at high incidences in Studies CRB-401 and MM-001. After Abecma infusion, patients should be monitored extremely carefully, and adverse events, if any, should be resolved by a multidisciplinary approach. Given that adverse events such as leukopenia were observed at higher incidences in Japanese patients than in non-Japanese patients, more careful adverse event management is required in Japanese patients, although the limited use experience with Abecma in Japanese patients precludes strict comparison of the safety of Abecma between Japanese and non-Japanese patients.

7.R.2.2 Safety profile of Abecma by event

PMDA reviewed the safety profile of Abecma based on the safety data from Studies CRB-401 and MM-001 with a focus on frequently observed events and serious events.

7.R.2.2.1 CRS

The applicant's explanation about (a) the incidence of CRS in the clinical studies, (b) risk factors of onset and aggravation of CRS, and (c) the management of CRS following Abecma infusion:
(a) Incidence of CRS in the clinical studies
Adverse events falling into the preferred term (PT) of "cytokine release syndrome" in the Medical Dictionary for Regulatory Activities (MedDRA) were investigated.

In Studies CRB-401 and MM-001, the grade definition of CRS based on Lee's criteria (*Blood.* 2014;124:188-95) shown in Table 27 was used.

Table 27. Grade definition of CRS

Grade 1	Mild symptoms Body temperature ≥38.5°C
Grade 2	Moderate symptoms Hypotension responsive to intravenous transfusion or low dose of a single vasopressor, or oxygen requirement (FiO_2) <40%, or Grade 2 organ toxicity
Grade 3	Severe symptoms Hypotension requiring high dose or multiple vasopressors, or oxygen requirement (FiO_2) ≥40%, or Grade 3 organ toxicity or Grade 4 hypertransaminasaemia
Grade 4	Life-threatening symptoms Requirement for ventilator support, or Grade 4 organ toxicity (excluding hypertransaminasaemia)
Grade 5	Death

Tables 28 and 29 show the incidences of CRS-related events in Studies MM-001 andCRB-401.

Table 28. Incidence of CRS
(Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

	Number of patients (%)		
	150×10^6 cells N = 4	300×10^6 cells N = 70	450×10^6 cells N = 63
All adverse events	2 (50.0)	53 (75.7)	61 (96.8)
Grade ≥3 adverse events	0	4 (5.7)	3 (4.8)
Serious adverse events	2 (50.0)	11 (15.7)	9 (14.3)
Adverse events leading to death	0	1 (1.4)	0
Median time to the first onset (range) (days)	7.0 (2-12)	2.0 (1-12)	1.0 (1-10)
Median duration of each event (range) (days)	5.0 (3-7) (2 events)	4.0 (2-28) (56 events)	6.5 (1-63) (64 events)

Table 29. Incidence of CRS (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

	Number of patients (%)			
	50×10^6 cells N = 3	150×10^6 cells N = 18	450×10^6 cells N = 38	800×10^6 cells N = 3
All adverse events	2 (66.7)	7 (38.9)	35 (92.1)	3 (100)
Grade ≥3 adverse events	0	0	3 (7.9)	1 (33.3)
Serious adverse events	1 (33.3)	3 (16.7)	7 (18.4)	2 (66.7)
Adverse events leading to death	0	0	0	0
Median time to the first onset (range) (days)	10.0 (1-19)	2.0 (1-17)	2.0 (1-11)	1.0 (1-4)
Median duration of each event (range) (days)	2.0 (1-3) (2 events)	4.0 (1-22) (11 events)	5.0 (1-32) (40 events)	4.5 (3-7) (4 events)

The incidence of CRS increased with the increase in the target dose. In patients receiving Abecma at the target dose of 450×10^6 cells, the median time to the first onset of CRS was shorter, and the median duration was longer, than in those receiving Abecma at the target dose of 150×10^6 or 300×10^6 cells.

Table 30 shows the characteristics of patients who experienced serious or Grade ≥3 CRS in Studies MM-001 and CRB-401.

In Study MM-001, fatal CRS was observed in 1 patient.[17)]

Table 30. List of patients experiencing serious or Grade ≥3 CRS (Studies MM-001 and CRB-401)

Age	Sex	Target dose	Grade	Seriousness	Causal relationship	Time to onset (days)	Duration (days)	Outcome	Treatment with tocilizumab/ number of treatments
Study MM-001									
4	Male	150	1	Serious	Related	12	7	Resolved	Untreated
6	Male	150	2	Serious	Related	2	3	Resolved	Treated/1
5	Female	300	3	Serious	Related	9	9	Resolved	Treated/3
			2	Serious	Related	17	12	Resolved	
5	Female	300	2	Serious	Related	1	5	Resolved	Treated/2
7	Male	300	2	Serious	Related	6	3	Resolved	Treated/2
6	Female	300	1	Serious	Related	15	5	Resolved	Untreated
4	Female	300	3	Serious	Related	2	2	Resolved	Treated/2
			4	Serious	Related	4	1	Resolved with sequelae	
			5	Serious	Related	5	1	Dead	
6	Male	300	1	Serious	Related	22	2	Resolved	Untreated
7	Female	300	3	Serious	Related	3	2	Resolved	Treated/1
3	Male	300	2	Serious	Related	3	2	Resolved	Untreated
4	Female	300	2	Serious	Related	2	3	Resolved	Treated/2
			2	Serious	Related	7	3	Resolved	
5	Male	300	1	Serious	Related	2	5	Resolved	Treated/3
			4	Serious	Related	7	6	Resolved	
5	Male	300	2	Serious	Related	4	4	Resolved	Treated/1
7	Female	450	2	Serious	Related	10	9	Resolved	Treated/1
6	Male	450	2	Serious	Related	6	8	Resolved	Treated/2
5	Male	450	3	Serious	Related	3	23	Resolved	Treated/2
5	Male	450	2	Serious	Related	1	2	Resolved	Treated/1
6	Female	450	1	Serious	Related	1	8	Resolved	Treated/2
4	Female	450	2	Serious	Related	1	10	Resolved	Treated/2
6	Female	450	2	Serious	Related	9	3	Resolved	Treated/3
4	Female	450	3	Serious	Related	2	4	Resolved	Treated/2
7	Male	450	3	Serious	Related	8	10	Resolved	Treated/2
Study CRB-401									
6	Male	50	1	Serious	Related	19	3	Resolved	Untreated
6	Female	150	1	Serious	Related	36	5	Resolved	Untreated
5	Female	150	1	Serious	Related	17	3	Resolved	Untreated
7	Male	150	2	Serious	Related	11	5	Resolved	Untreated
6	Male	450	1	Serious	Related	3	12	Resolved	Untreated
5	Female	450	1	Serious	Related	18	5	Resolved	Untreated
4	Female	450	1	Serious	Related	2	2	Resolved	Treated/1
4	Female	450	3	Serious	Related	11	32	Resolved	Treated/1
5	Male	450	3	Serious	Related	4	3	Resolved	Treated/1
6	Female	450	1	Serious	Related	4	2	Resolved	Untreated
			2	Serious	Related	5	2	Resolved	
			1	Serious	Related	6	2	Resolved	
3	Male	450	3	Serious	Related	6	2	Resolved	Treated/1
6	Female	800	2	Serious	Related	12	7	Resolved	Treated/1
5	Female	800	3	Serious	Related	4	2	Resolved	Treated/1

(b) Risk factors of onset and aggravation of CRS

CRS is defined as a systemic inflammatory reaction caused by inflammatory cytokines (e.g., IFN-γ) released by various activated lymphocytes (B cells, T cells, natural killer cells [NK cells], etc.) and myeloid cells. High tumor volume and high inflammatory cytokine level at baseline are related to increased incidence of CRS (*Bone Marrow Transplant.* 2019;54:780-4).

In Study MM-001, the percentage of patients with high tumor volume (CD138-positive plasma cells in bone marrow ≥50%) at baseline was 51.7% in patients who experienced CRS, which was higher than the percentage in patients without CRS (38.1%). No relationship was observed between the occurrence

of CRS and immune-related soluble factors or inflammatory markers (C-reactive protein [CRP] and ferritin).

(c) CRS management algorithm

Table 31 shows the outline of the CRS management algorithm in Studies CRB-401 and MM-001.

Table 31. Outline of CRS management algorithm (Studies CRB-401 and MM-001)

	Management method
After Abecma administration	• Monitor for CRS symptoms (pyrexia, hemodynamic instability, hypoxia) according to the protocol and perform neurological evaluation. • Monitor serum CRP, ferritin, and coagulation parameters. • Consider hospitalization for close monitoring.
First-line treatment (a) Pyrexia of ≥38.5°C or any Grade ≥2 CRS sign or symptom <72 hours after Abecma infusion (b) Pyrexia of ≥38°C ≥72 hours after Abecma infusion and CRS clinically progressed or rapidly aggravated after symptomatic treatment, etc.	Grade 1 CRS: (a) Consider intravenous administration of tocilizumab 8 mg/kg (alone or in combination with dexamethasone 10 mg 24 hours apart). (b) Provide symptomatic treatment. Grade 2 CRS: (a) Administer tocilizumab 8 mg/kg and dexamethasone 10 mg (12-24 hours apart) intravenously. (b) Administer tocilizumab 8 mg/kg (alone or in combination with dexamethasone 10 mg 12-24 hours apart) intravenously. Grade 3 CRS: • Administer tocilizumab 8 mg/kg and dexamethasone 10 mg (12 hours apart) intravenously. Grade 4 CRS: • Administer tocilizumab 8 mg/kg and dexamethasone 20 mg (6 hours apart) intravenously.
	For CRS unimproved or rapidly progressed within 24 hours of the first line treatment: • Start the second line treatment.
Second-line treatment	• Administer the second dose of tocilizumab 8 mg/kg and dexamethasone 20 mg (6-12 hours apart) intravenously. • Search for other causes of clinical aggravation (e.g., sepsis, adrenal insufficiency).
	For CRS unimproved or rapidly progressed within 24 hours of the second-line treatment: • Start the third-line treatment.
Third-line treatment	• Administer methylprednisolone 2 mg/kg, followed by a total of 2 mg/kg in 4 divided doses per day (to be tapered off within 7 days). • Consider using other anti-IL-6 drugs.
	For CRS persisting even after the above treatments: • Start the fourth-line treatment.
Fourth-line treatment	• Consider anti-T cell therapy with cyclophosphamide 1.5 g/m^2, etc.
Other considerations	• Dexamethasone, once started, should be administered ≥3 times or until the disappearance of CRS and related neurological symptoms. Grade 1 CRS: • Consider convulsive seizure prevention (e.g., administration of levetiracetam). Grade 2 CRS: • Frequently monitor the patient under the hospitalized conditions until pyrexia and symptoms resolve. Perform neurological evaluation and symptomatic therapies (oxygen supplementation, intravenous transfusion and aggressive electrolyte replenishment, antipyretics, and low-dose vasopressor). Start convulsive seizure prevention (e.g., administration of levetiracetam) if neurologic toxicity is observed and consider monitoring of electroencephalogram. Grade ≥3 CRS: • Perform monitoring, symptomatic treatment, hemodynamic and respiratory assistance, and neurological evaluation at ICU. Start convulsive seizure prevention (e.g., administration of levetiracetam) if neurologic toxicity is observed and consider monitoring of electroencephalogram.

PMDA's view:

In the clinical studies, CRS occurred frequently after Abecma administration with some serious cases. In addition, CRS occurred 1 to 2 days after the Abecma administration. Given these, Abecma treatment requires hospitalization and close monitoring particularly during the early post-treatment phase. The incidence of CRS and the method for CRS management practiced in the clinical studies should be

appropriately communicated to healthcare professionals via the package insert to call attention. Furthermore, Abecma must be administered by a physician with sufficient knowledge and experience in systemic control on hematopoietic malignancy and critical conditions such as CRS at a medical institution with an intensive care unit (ICU), etc. for immediate systemic control in emergencies. This should also be advised via the package insert, etc.

7.R.2.2.2 Haemophagocytic lymphohistiocytosis

The applicant's explanation about haemophagocytic lymphohistiocytosis caused by Abecma administration:

Adverse events falling under the MedDRA PT[23)] of "Haemophagocytic lymphohistiocytosis" are listed in Table 32.

In Study MM-001, haemophagocytic lymphohistiocytosis was observed in 5 patients (3.6%); in 1 patient receiving 300×10^6 cells and in 4 patients (including 1 Japanese patient) receiving 450×10^6 cells. Severity was Grade 2 in 3 patients and Grade 4 in 2 patients, and all of the events occurred within 8 weeks after Abecma administration.

No haemophagocytic lymphohistiocytosis was observed in Study CRB-401.

Table 32. List of patients with haemophagocytic lymphohistiocytosis (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

Age	Sex	Target dose	Grade	Seriousness	Causal relationship	Time to onset (days)	Duration (days)	Occurrence of CRS	Outcome
4[redacted]	Female	300	4	Nonserious	Related	4	—	Yes	Unresolved
6[redacted]	Female	450	2	Serious	Related	5	4	Yes	Resolved
6[redacted]	Female	450	2	Nonserious	Related	9	3	Yes	Resolved
7[redacted]	Male	450	4	Serious	Related	9	—	Yes	Unresolved
4[redacted]	Male	450	2	Nonserious	Related	2	21	Yes	Resolved

PMDA's view:

The clinical studies of Abecma identified serious haemophagocytic lymphohistiocytosis in which its causal relationship to Abecma could not be ruled out. In addition, haemophagocytic lymphohistiocytosis was observed with approved anti-CD19 CAR-expressing T cell therapy as well. Therefore, caution should be exercised against haemophagocytic lymphohistiocytosis when Abecma is administered. Accordingly, the package insert, etc. should provide and caution healthcare professionals with information about haemophagocytic lymphohistiocytosis appropriately, including its occurrence in the clinical studies, to advise on appropriate measures to be taken in case of the event.

7.R.2.2.3 Neurologic toxicity

The applicant's explanation about neurologic toxicity associated with Abecma:

Adverse events falling under the MedDRA system organ class (SOC) of "Nervous system disorders" or "Psychiatric disorders" were counted as neurologic toxicity. Tables 33 to 36 show the incidences of neurologic toxicity in Studies MM-001 and CRB-401. In addition to the above events, asthenia (PT) in

23) Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.22.0

2 patients receiving 300 × 10^6 cells in Study MM-001 was reported as neurologic toxicity[10] identified by the investigator, but both were non-serious and Grade 1.

Table 33. Incidence of neurologic toxicity (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

	Number of patients (%)		
	150 × 10^6 cells N= 4	300 × 10^6 cells N = 70	450 × 10^6 cells N = 63
All adverse events	2 (50.0)	56 (80.0)	33 (52.4)
Grade ≥3 adverse events	0	9 (12.9)	9 (14.3)
Serious adverse events	0	12 (17.1)	11 (17.5)
Adverse events leading to death	0	1 (1.4)	1 (1.6)
Median time to the first onset (range) (days)	51.5 (42-61)	5.0 (1-604)	6.0 (1-720)

Table 34. Incidence of neurologic toxicity (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

	Number of patients (%)			
	50 × 10^6 cells N = 3	150 × 10^6 cells N = 18	450 × 10^6 cells N = 38	800 × 10^6 cells N = 3
All adverse events	1 (33.3)	14 (77.8)	29 (76.3)	3 (100)
Grade ≥3 adverse events	0	1 (5.6)	6 (15.8)	0
Serious adverse events	0	1 (5.6)	3 (7.9)	0
Adverse events leading to death	0	0	0	0
Median time to the first onset (range) (days)	6.0	9.5 (2-95)	5.0 (1-451)	11.0 (3-126)

Table 35. Neurologic toxicity reported by ≥5% of patients at any target dose (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

PT (MedDRA/J Version22.0)	Number of patients (%)					
	150 × 10^6 cells N = 4		300 × 10^6 cells N = 70		450 × 10^6 cells N = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Headache	1 (25.0)	0	19 (27.1)	1 (1.4)	8 (12.7)	0
Dizziness	1 (25.0)	0	13 (18.6)	0	4 (6.3)	0
Encephalopathy	0	0	2 (2.9)	1 (1.4)	6 (9.5)	3 (4.8)
Anxiety	0	0	11 (15.7)	0	2 (3.2)	1 (1.6)
Confusional state	0	0	10 (14.3)	2 (2.9)	7 (11.1)	0
Insomnia	0	0	8 (11.4)	0	3 (4.8)	0
Tremor	1 (25.0)	0	7 (10.0)	0	2 (3.2)	0
Vision blurred	0	0	5 (7.1)	0	0	0
Aphasia	0	0	4 (5.7)	0	3 (4.8)	1 (1.6)
Paraesthesia	0	0	4 (5.7)	1 (1.4)	0	0
Sleep disorder	0	0	4 (5.7)	0	1 (1.6)	0
Somnolence	1 (25.0)	0	4 (5.7)	0	3 (4.8)	0

Table 36. Neurologic toxicity reported by ≥10% of patients at any target dose (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

PT (MedDRA/J Version22.0)	Number of patients (%)							
	50×10^6 cells N = 3		150×10^6 cells N = 18		450×10^6 cells N = 38		450×10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Headache	1 (33.3)	0	5 (27.8)	0	12 (31.6)	0	0	0
Dizziness	0	0	3 (16.7)	0	8 (21.1)	1 (2.6)	2 (66.7)	0
Neurotoxicity	0	0	1 (5.6)	0	6 (15.8)	1 (2.6)	0	0
Insomnia	0	0	2 (11.1)	0	5 (13.2)	0	1 (33.3)	0
Syncope	0	0	1 (5.6)	1 (5.6)	4 (10.5)	2 (5.3)	0	0
Tremor	0	0	1 (5.6)	0	4 (10.5)	0	0	0
Paraesthesia	1 (33.3)	0	0	0	2 (5.3)	0	0	0
Vision blurred	0	0	0	0	2 (5.3)	0	1 (33.3)	0
Muscular weakness	0	0	3 (16.7)	0	1 (2.6)	0	0	0
Gait disturbance	0	0	2 (11.1)	0	1 (2.6)	0	0	0
Depression	0	0	1 (5.6)	0	1 (2.6)	0	1 (33.3)	0
Neuropathy peripheral	0	0	1 (5.6)	0	0	0	1 (33.3)	0
Numb chin syndrome	1 (33.3)	0	0	0	0	0	0	0

Death due to neurologic toxicity occurred in 2 patients (cerebellar haemorrhage in 1 patient receiving 300×10^6 cells, cerebral haematoma in 1 patient receiving 450×10^6 cells) in Study MM-001, but its causal relationship to Abecma was ruled out in both of them.

Table 37 shows the characteristics of the patients who experienced Grade ≥3 neurologic toxicity in Studies MM-001 and CRB-401.

Table 37. List of patients experiencing Grade ≥3 neurologic toxicity

Age	Sex	Target dose	PT (MedDRA/J ver.22.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to Abecma	Outcome
Study MM-001									
4[redacted]	Female	300	Herpes zoster	3	Serious	149	37	Not related	Resolved
6[redacted]	Female	300	Syncope	3	Serious	528	3	Not related	Resolved
6[redacted]	Male	300	Spinal pain	3	Serious	37	3	Not related	Resolved
4[redacted]	Female	300	Syncope	3	Serious	217	1	Not related	Resolved
7[redacted]	Male	300	Confusional state	3	Serious	61	5	Not related	Resolved
6[redacted]	Female	300	Paraesthesia	3	Serious	236	2	Not related	Resolved
6[redacted]	Female	300	Confusional state	3	Serious	2	2	Related	Resolved
			Encephalopathy	3	Serious	2	2	Related	Resolved
6[redacted]	Female	300	Headache	3	Serious	155	7	Not related	Resolved
7[redacted]	Male	300	Cerebral haemorrhage	4	Serious	604	4	Not related	Resolved with sequelae
			Cerebral haemorrhage	5	Serious	607	1	Not related	Dead
6[redacted]	Male	450	Aphasia	3	Serious	6	2	Related	Resolved
			Hemiparesis	3	Serious	6	2	Related	Resolved
			Lethargy	3	Serious	6	2	Related	Resolved
			Metabolic encephalopathy	3	Serious	6	2	Related	Resolved
7[redacted]	Female	450	Mental status changes	3	Serious	4	2	Related	Resolved
5[redacted]	Male	450	Spinal cord compression	3	Serious	26	30	Not related	Resolved with sequelae
7[redacted]	Female	450	Adult failure to thrive	3	Serious	554	4	Not related	Resolved
6[redacted]	Male	450	Encephalopathy	3	Serious	226	26	Not related	Resolved
6[redacted]	Female	450	Encephalopathy	3	Serious	4	11	Related	Resolved with sequelae
7[redacted]	Male	450	Encephalopathy	3	Serious	6	5	Related	Resolved
5[redacted]	Male	450	Cerebral haematoma	4	Serious	554	1	Not related	Resolved with sequelae
			Cerebral haematoma	5	Serious	555	1	Not related	Dead
5[redacted]	Male	450	Anxiety	3	Nonserious	69	1	Not related	Resolved
Study CRB-401									
6[redacted]	Female	150	Syncope	3	Serious	37	1	Related	Resolved
			Syncope	3	Serious	354	1	Not related	Resolved
			Syncope	3	Serious	474	1	Not related	Resolved
6[redacted]	Female	450	Urinary incontinence	3	Nonserious	2	14	Not related	Resolved
5[redacted]	Male	450	Delirium	3	Nonserious	105	6	Not related	Resolved
6[redacted]	Male	450	Subdural haematoma	3	Serious	51	5	Not related	Resolved with sequelae
4[redacted]	Female	450	Neurotoxicity	4	Serious	11	32	Related	Resolved
			Subarachnoid haemorrhage	4	Serious	14	33	Related	Resolved
4[redacted]	Male	450	Syncope	3	Nonserious	91	1	Not related	Resolved
			Dizziness	3	Nonserious	94	30	Not related	Resolved
6[redacted]	Male	450	Syncope	3	Nonserious	451	1	Not related	Resolved

PMDA's view:

Caution should be exercised against Abecma-associated neurologic toxicity because neurologic toxicity was observed at a high frequency in the clinical studies with some serious or Grade ≥3 cases, and the patient should be carefully monitored after Abecma infusion. Accordingly, the incidence of neurologic

toxicity in the clinical studies and their breakdown should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention.

7.R.2.2.4 Infection

The applicant's explanation about infection associated with Abecma:

Adverse events falling under the MedDRA SOC of "Infections and infestations" were counted as infections and are listed in Tables 38 to 41. In Studies MM-001 and CRB-401, trimethoprim-sulfamethoxazole combination therapy, etc., was recommended to prevent *Pneumocystis* pneumonia in patients with CD4-positive T cell count of <200/μL. Also, the study protocol specified that prophylactic, pre-emptive, or symptomatic treatment with antibacterial, antifungal, anti-Pneumocystis, or antiviral drugs should be considered.[24)]

Table 38. Incidence of infection (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

Classification	Number of patients (%)		
	150×10^6 cells N = 4	300×10^6 cells N = 70	450×10^6 cells N = 63
All infections	3 (75.0)	48 (68.6)	44 (69.8)
Infection-bacteria	0	6 (8.6)	16 (25.4)
Infection-viruses	3 (75.0)	19 (27.1)	19 (30.2)
Infection-fungi	0	6 (8.6)	4 (6.3)
Infection-pathogen unidentified	2 (50.0)	35 (50.0)	28 (44.4)

Table 39. Incidence of infection (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

Classification	Number of patients (%)			
	50×10^6 cells N = 3	150×10^6 cells N = 18	450×10^6 cells N = 38	800×10^6 cells N = 3
All infections	2 (66.7)	13 (72.2)	29 (76.3)	3 (100)
Infection-bacteria	0	0	6 (15.8)	1 (33.3)
Infection-viruses	1 (33.3)	2 (11.1)	10 (26.3)	0
Infection-fungi	0	1 (5.6)	0	0
Infection-pathogen unidentified	2 (66.7)	12 (66.7)	24 (63.2)	3 (100)

[24)] In Study MM-001, the following prophylactic medications were given: Antibacterial agent in 72.3% of patients, trimethoprim-sulfamethoxazole in 40.1% of patients, antifungal drug in 46.0% of patients, and antiviral drug in 73.7% of patients. In Study CRB-401, the following prophylactic medications were given: Antibacterial agent in 83.9% of patients, trimethoprim-sulfamethoxazole in 48.4% of patients, antifungal drug in 33.9% of patients, and antiviral drug in 98.4% of patients.

Table 40. Infection reported by ≥5% of patients at any target dose (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

PT (MedDRA/J ver.22.0)	Number of patients (%)					
	150×10^6 cells N = 4		300×10^6 cells N = 70		450×10^6 cells N = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	3 (75.0)	1 (25.0)	48 (68.6)	16 (22.9)	44 (69.8)	18 (28.6)
Influenza	1 (25.0)	0	2 (2.9)	0	9 (14.3)	4 (6.3)
Pneumonia	0	0	8 (11.4)	4 (5.7)	8 (12.7)	5 (7.9)
Upper respiratory tract infection	0	0	13 (18.6)	0	7 (11.1)	1 (1.6)
Bronchitis	0	0	0	0	4 (6.3)	0
Gastroenteritis	0	0	1 (1.4)	1 (1.4)	4 (6.3)	0
Nasopharyngitis	0	0	3 (4.3)	0	4 (6.3)	0
Sepsis	0	0	4 (5.7)	4 (5.7)	4 (6.3)	3 (4.8)
Arthritis infective	1 (25.0)	1 (25.0)	0	0	0	0
Candida infection	0	0	4 (5.7)	0	1 (1.6)	0
Corona virus infection	0	0	4 (5.7)	1 (1.4)	1 (1.6)	0
Respiratory syncytial virus infection	0	0	4 (5.7)	0	0	0
Enterovirus infection	1 (25.0)	0	0	0	0	0
Rhinovirus infection	1 (25.0)	1 (25.0)	4 (5.7)	0	1 (1.6)	0
Sinusitis	1 (25.0)	0	5 (7.1)	0	1 (1.6)	0
Urinary tract infection	0	0	5 (7.1)	1 (1.4)	2 (3.2)	0

Table 41. Infection reported by ≥10% of patients at any target dose (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

PT (MedDRA/J ver.22.0)	Number of patients (%)							
	50×10^6 cells N = 3		150×10^6 cells N = 18		450×10^6 cells N = 38		800×10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	2 (66.7)	0	13 (72.2)	3 (16.7)	29 (76.3)	9 (23.7)	3 (100)	3 (100)
Upper respiratory tract infection	2 (66.7)	0	8 (44.4)	1 (5.6)	13 (34.2)	3 (7.9)	1 (33.3)	0
Lung infection	0	0	2 (11.1)	2 (11.1)	1 (2.6)	1 (2.6)	0	0
Respiratory syncytial virus infection	1 (33.3)	0	2 (11.1)	0	2 (5.3)	0	0	0
Urinary tract infection	0	0	2 (11.1)	0	7 (18.4)	0	0	0
Arthritis reactive	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Pneumonia	0	0	0	0	3 (7.9)	2 (5.3)	1 (33.3)	1 (33.3)
Pneumonia bacterial	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Respiratory tract infection	0	0	0	0	0	0	1 (33.3)	0

Fatal infection was observed in 6 patients in Study MM-001 (sepsis and pneumonia cytomegaloviral in 1 patient each at 300×10^6 cells; pneumonia in 2 patients, and bronchopulmonary aspergillosis and septic shock in 1 patient each at 450×10^6 cells).

In Study MM-001, serious infection was observed in 37 patients (1 patient at 150×10^6 cells, 16 patients at 300×10^6 cells, 20 patients at 450×10^6 cells). Serious infections observed in ≥2 subjects were pneumonia in 12 patients (5 patients at 300×10^6 cells, 7 patients at 450×10^6 cells), sepsis in 7 patients (4 patients at 300×10^6 cells, 3 patients at 450×10^6 cells), influenza in 4 patients (4 patients at 450×10^6 cells), respiratory tract infection in 2 patients (1 patient at 300×10^6 cells, 1 patient at 450×10^6 cells), Clostridium difficile colitis in 2 patients (1 patient at 300×10^6 cells, 1 patient at 450×10^6 cells), hepatitis E in 2 patients (2 patients at 450×10^6 cells), Pneumonia pseudomonal in 2 patients (2 patients at 450×10^6 cells), and Rhinovirus infection in 2 patients (1 patient at 150×10^6 cells, 1 patient at 300×10^6 cells). In Study CRB-401, serious infection was observed in 16 patients (4 of 18 patients at 150×10^6 cells, 9 of 38 patients at 450×10^6 cells, 3 of 3 patients at 800×10^6 cells). Serious infections observed in ≥2 patients among all patients were lung infection in 3 patients (2 patients at 150×10^6 cells, 1 patient

at 450 × 10^6 cells), upper respiratory tract infection in 2 patients (2 patients at 450 × 10^6 cells), and pneumonia in 2 patients (1 patient at 450 × 10^6 cells, 1 patient at 800 × 10^6 cells).

PMDA's view:
Caution should be exercised against Abecma-associated infection because fatal infection, Grade ≥3 infection, and serious infection have been observed in the clinical studies. Accordingly, the incidence of infection in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention.

7.R.2.2.5 Cytopenia

The applicant's explanation about cytopenia associated with Abecma:
Events related to cytopenia were classified into neutropenia, anaemia, thrombocytopenia, lymphopenia, and pancytopenia as shown in Table 42. Tables 43 and 44 show the incidences of these classified events.

Table 42. List of events included in cytopenia

Classification	MedDRA PT (MedDRA/J version 22.0)
Neutropenia	Neutropenia, Leukopenia, Febrile neutropenia, Neutrophil count decreased, White blood cell count decreased, Autoimmune neutropenia, Agranulocytosis, Cyclic neutropenia, Granulocyte count decreased, Granulocytopenia, Idiopathic neutropenia, Myelocyte count decreased, Myelocyte percentage decreased, Neutrophil percentage decreased, White blood cell analysis abnormal
Anaemia	Anaemia, Anaemia macrocytic, Anaemia megaloblastic, Haematocrit decreased, Haemoglobin decreased, Hyperchromic anaemia, Hypochromic anaemia, Leukoerythroblastic anaemia, Mean cell haemoglobin concentration decreased, Mean cell haemoglobin decreased, Mean cell volume decreased, Microcytic anaemia, Normochromic anaemia, Normochromic normocytic anaemia, Normocytic anaemia, Proerythroblast count decreased, Red blood cell count decreased, Reticulocyte count decreased, Reticulocyte percentage decreased, Sideroblastic anaemia
Thrombocytopenia	Thrombocytopenia, Platelet count decreased, Immune thrombocytopenic purpura, Acquired amegakaryocytic thrombocytopenia, Amegakaryocytic thrombocytopenia, Heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia test positive, Non-immune heparin associated thrombocytopenia, Platelet production decreased, Severe fever with thrombocytopenia syndrome, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura
Lymphopenia	Lymphopenia, CD4 lymphocytes decreased, B-lymphocyte abnormalities, B-lymphocyte count abnormal, B-lymphocyte count decreased, CD4 lymphocyte percentage decreased, CD4 lymphocytes abnormal, CD4/CD8 ratio decreased, CD8 lymphocyte percentage decreased, CD8 lymphocytes abnormal, CD8 lymphocytes decreased, Lymphocyte count decreased, Lymphocyte percentage decreased, Natural killer T cell count decreased, Plasma cells absent, Plasma cells decreased, Plasmablast count decreased, T-lymphocyte count decreased
Pancytopenia	Pancytopenia, Autoimmune aplastic anaemia, Autoimmune pancytopenia, Aplasia pure red cell, Aplastic anaemia, Bicytopenia, Bone marrow failure, Bone marrow toxicity, Cytopenia, Erythroid maturation arrest, Febrile bone marrow aplasia, Granulocytes maturation arrest, Hypoplastic anaemia, Myeloid maturation arrest, Panmyelopathy, Platelet maturation arrest, Pure white cell aplasia

Table 43. Cytopenia reported by ≥5% of patients at any target dose (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

Classification PT (MedDRA/J ver.22.0)	Number of patients (%)					
	150×10^6 cells N = 4		300×10^6 cells N = 70		450×10^6 cells N = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cytopenia - Neutropenia	4 (100)	4 (100)	66 (94.3)	64 (91.4)	60 (95.2)	60 (95.2)
Neutropenia	4 (100)	4 (100)	62 (88.6)	59 (84.3)	60 (95.2)	60 (95.2)
Febrile neutropenia	2 (50.0)	2 (50.0)	11 (15.7)	11 (15.7)	9 (14.3)	8 (12.7)
Leukopenia	2 (50.0)	2 (50.0)	34 (48.6)	30 (42.9)	26 (41.3)	26 (41.3)
Neutrophil count decreased	1 (25.0)	1 (25.0)	3 (4.3)	3 (4.3)	0	0
Cytopenia - Anaemia	4 (100)	4 (100)	51 (72.9)	42 (60.0)	40 (63.5)	37 (58.7)
Anaemia	4 (100)	4 (100)	51 (72.9)	42 (60.0)	40 (63.5)	37 (58.7)
Cytopenia - Thrombocytopenia	4 (100)	3 (75.0)	45 (64.3)	36 (51.4)	42 (66.7)	36 (57.1)
Thrombocytopenia	4 (100)	3 (75.0)	42 (60.0)	34 (48.6)	42 (66.7)	36 (57.1)
Cytopenia - Lymphopenia	2 (50.0)	2 (50.0)	20 (28.6)	20 (28.6)	24 (38.1)	21 (33.3)
Lymphopenia	2 (50.0)	2 (50.0)	19 (27.1)	19 (27.1)	22 (34.9)	21 (33.3)

Table 44. Cytopenia reported by ≥10% of patients at any target dose (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

Classification PT (MedDRA/J ver.22.0)	Number of patients (%)							
	50×10^6 cells N = 3		150×10^6 cells N = 18		450×10^6 cells N = 38		800×10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Cytopenia - Neutropenia	3 (100)	3 (100)	17 (94.4)	16 (88.9)	35 (92.1)	34 (89.5)	3 (100)	3 (100)
Neutropenia	3 (100)	3 (100)	16 (88.9)	15 (83.3)	35 (92.1)	34 (89.5)	3 (100)	3 (100)
Leukopenia	3 (100)	3 (100)	12 (66.7)	11 (61.1)	23 (60.5)	22 (57.9)	2 (66.7)	2 (66.7)
Febrile neutropenia	0	0	3 (16.7)	2 (11.1)	6 (15.8)	5 (13.2)	1 (33.3)	1 (33.3)
Cytopenia - Anaemia	3 (100)	2 (66.7)	11 (61.1)	6 (33.3)	30 (78.9)	24 (63.2)	3 (100)	3 (100)
Anaemia	3 (100)	2 (66.7)	11 (61.1)	6 (33.3)	30 (78.9)	24 (63.2)	3 (100)	3 (100)
Cytopenia - Thrombocytopenia	2 (66.7)	2 (66.7)	13 (72.2)	10 (55.6)	29 (76.3)	22 (57.9)	2 (66.7)	2 (66.7)
Thrombocytopenia	2 (66.7)	2 (66.7)	13 (72.2)	10 (55.6)	29 (76.3)	21 (55.3)	2 (66.7)	2 (66.7)
Cytopenia - Lymphopenia	0	0	8 (44.4)	8 (44.4)	16 (42.1)	15 (39.5)	0	0
Lymphopenia	0	0	7 (38.9)	7 (38.9)	16 (42.1)	15 (39.5)	0	0

Tables 45 and 46 show the rime to the first onset and the duration of cytopenia.

Table 45. Time to the first onset and duration of cytopenia (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

Classification (MedDRA/J ver.22.0)	Median (days) (range) (days)					
	150×10^6 cells		300×10^6 cells		450×10^6 cells	
	Time to onset*	Duration	Time to onset*	Duration	Time to onset*	Duration
Cytopenia - Neutropenia	1.5 (1-2)	8.5 (5-21)	1.0 (1-205)	10.0 (1-261)	1.0 (1-30)	11.5 (1-351)
Cytopenia - Anaemia	6.0 (2-15)	69.0 (2-101)	3.0 (1-181)	9.0 (1-307)	3.0 (1-501)	10.0 (1-327)
Cytopenia - Thrombocytopenia	7.5 (2-61)	17.0 (1-39)	3.0 (1-236)	35.0 (2-284)	5.0 (1-631)	19.0 (3-427)
Cytopenia - Lymphopenia	10.5 (9-12)	26.0 (14-38)	7.5 (1-241)	22.0 (2-256)	8.0 (1-518)	10.0 (1-541)

* Days after Abecma administration

Table 46. Time to the first onset and duration of cytopenia (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

Classification (MedDRA/J ver.22.0)	Median (days) (range) (days)							
	50×10^6 cells		150×10^6 cells		450×10^6 cells		800×10^6 cells	
	Time to onset*	Duration	Time to onset*	Duration	Time to onset*	Duration	Time to onset*	Duration
Cytopenia - Neutropenia	3.0 (1-6)	5.0 (3-7)	1.0 (1-8)	8.0 (1-32)	1.0 (1-17)	9.0 (1-449)	2.0 (2-4)	8.0 (5-10)
Cytopenia - Anaemia	2.0 (2-120)	11.0 (1-21)	3.0 (1-278)	24.5 (2-176)	3.0 (1-268)	18.0 (1-175)	1.0 (1-24)	10.0 (8-125)
Cytopenia - Thrombocytopenia	64.5 (9-120)	51.0	8.0 (1-352)	31.0 (3-93)	3.0 (1-78)	33.0 (2-375)	16.0 (8-24)	29.0 (8-50)
Cytopenia - Lymphopenia	—	—	6.0 (2-319)	9.0 (1-113)	7.5 (1-197)	26.0 (2-455)	—	—

* Days after Abecma administration

There was no fatal cytopenia either in Study MM-001 or in Study CRB-401.

Serious cytopenia was observed in 20 of 137 patients (14.6%) in Study MM-001, i.e., febrile neutropenia in 9 patients (2 patients at 150×10^6 cells, 5 patients at 300×10^6 cells, 2 patients at 450×10^6 cells), neutropenia in 6 patients (2 patients at 300×10^6 cells, 4 patients at 450×10^6 cells), anaemia in 1 patient (at 300×10^6 cells), thrombocytopenia in 7 patients (2 patients at 300×10^6 cells, 5 patients at 450×10^6 cells), and pancytopenia in 1 patient (at 450×10^6 cells). In Study CRB-401, serious cytopenia was observed in 5 of 62 patients (8.1%), i.e., neutropenia in 2 patients (at 150×10^6 cells), leukopenia in 1 patient (at 150×10^6 cells), febrile neutropenia in 2 patients (at 450×10^6 cells), anaemia in 1 patient (at 800×10^6 cells), and thrombocytopenia in 1 patient (at 150×10^6 cells).

PMDA's view:
Caution should be exercised against Abecma-associated cytopenia because serious cytopenia events have been observed in the clinical studies. Accordingly, information including the occurrence and time to onset of cytopenia in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. In addition, the following cautionary advice should be appropriately provided to healthcare professionals via the package insert, etc. to call attention: Blood tests should be performed regularly after Abecma infusion, and appropriate measures should be taken for cytopenia, once detected.

7.R.2.2.6 Hypersensitivity

The applicant's explanation about hypersensitivity associated with Abecma:

Adverse events falling under the MedDRA standardised MedDRA queries (SMQ) (narrow) of "Hypersensitivity" in Study MM-001 are listed in Table 47. The protocols of the clinical studies on Abecma specified that subjects must receive premedication with acetaminophen and diphenhydramine hydrochloride approximately 30 minutes prior to Abecma infusion.

Table 47. Incidences of hypersensitivity
(Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

PT (MedDRA/J ver.22.0)	Number of patients (%)					
	150×10^6 cells N = 4		300×10^6 cells N = 70		450×10^6 cells N = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity	1 (25.0)	0	15 (21.4)	1 (1.4)	16 (25.4)	3 (4.8)
Rash	0	0	4 (5.7)	0	7 (11.1)	1 (1.6)
Infusion related reaction	0	0	5 (7.1)	0	3 (4.8)	0
Urticaria	0	0	0	0	2 (3.2)	1 (1.6)
Angioedema	0	0	0	0	1 (1.6)	0
Dermatitis bullous	0	0	0	0	1 (1.6)	0
Distributive shock	0	0	0	0	1 (1.6)	1 (1.6)
Eye oedema	0	0	0	0	1 (1.6)	0
Scrotal oedema	0	0	2 (2.9)	0	0	0
Bronchospasm	0	0	1 (1.4)	1 (1.4)	0	0
Dermatitis	0	0	1 (1.4)	0	0	0
Periorbital oedema	1 (25.0)	0	0	0	0	0
Face oedema	0	0	1 (1.4)	0	1 (1.6)	0
Hypersensitivity	0	0	1 (1.4)	0	1 (1.6)	0
Rash macular	0	0	1 (1.4)	0	0	0
Rhinitis allergic	0	0	1 (1.4)	0	0	0

Table 48 shows characteristics of the patients who experienced serious or Grade ≥3 hypersensitivity in Study MM-001. No fatal hypersensitivity was observed.

Table 48. List of patients with serious or Grade ≥3 hypersensitivity

Age	Sex	Target dose	PT (MedDRA/J ver.22.0)	Grade	Seriousness	Causal relationship to Abecma	Time to onset (days)	Duration (days)	Outcome
7[redacted]	Male	300	Bronchospasm	3	Nonserious	Not related	6	1	Resolved
5[redacted]	Male	450	Urticaria	3	Serious	Not related	169	4	Resolved with sequelae
5[redacted]	Male	450	Distributive shock	4	Serious	Related	30	—	Unresolved
5[redacted]	Female	450	Rash	3	Serious	Not related	449	23	Resolved

In Study CRB-401, hypersensitivity was observed in 1 of 3 patients (33.3%; rash maculo-papular) at the target dose of 50×10^6 cells, in 5 of 18 patients (27.8%; rash maculo-papular in 2 patients, gingival swelling, infusion related reaction and rhinitis allergic in 1 patient each) at the target dose of 150×10^6 cells, in 6 of 38 patients (15.8%; rash in 4 patients, eczema and rhinitis allergic in 1 patient each) at the target dose of 450×10^6 cells, and in 1 of 3 patients (33.3%; rash maculo-papular and swelling face) at the target dose of 800×10^6 cells. No Grade ≥3 or serious hypersensitivity were observed.

In the ongoing Study BB2121-MM-002 (Study MM-002),[25] a serious adverse event (laryngeal oedema) was reported in 1 patient. Four hypersensitivity events occurred from Day 21 to Day 52 at the target dose of 450 × 10^6 cells, and they were assessed to be causally related to Abecma. The outcome was "recovered" in all of them.

PMDA's review:
Caution should be exercised against Abecma-associated hypersensitivity because Grade ≥3 or serious hypersensitivity occurred after Abecma infusion. Accordingly, the incidence of hypersensitivity in the clinical studies and the protocol-specified premedication in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention.

7.R.2.2.7 Hypogammaglobulinaemia

The applicant's explanation about hypogammaglobulinaemia associated with Abecma:
Adverse events falling under the MedDRA PT of "Hypogammaglobulinaemia" were counted.

In Study MM-001, hypogammaglobulinaemia was observed in 1 of 4 patients (25.0%) at the target dose of 150 × 10^6 cells, in 15 of 70 patients (21.4%) at 300 × 10^6 cells, and in 15 of 63 patients (23.8%) at 450 × 10^6 cells. Grade ≥3 events were observed in 2 of 63 patients (3.2%) at 450 × 10^6 cells (including 1 Japanese patient). In Study CRB-401, hypogammaglobulinaemia was observed in 4 of 18 patients (22.2%) at 150 × 10^6 cells and in 5 of 38 patients (13.2%) at 450 × 10^6 cells. No Grade ≥3 events were observed. No fatal or serious hypogammaglobulinaemia was observed in either study.

PMDA's view:
Caution should be exercised against Abecma-associated hypogammaglobulinaemia because (1) Grade ≥3 hypogammaglobulinaemia occurred in patients receiving Abecma in the clinical studies, (2) hypogammaglobulinaemia is an attention-calling event of an approved anti-CD19 CAR-expressing T cell therapy, and (3) anti-BCMA CAR-expressing T cell infusion may cause B cell depletion in the body. Accordingly, the incidence of hypogammaglobulinaemia in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention so that appropriate measures are taken in case of hypogammaglobulinaemia.

7.R.2.2.8 TLS

The applicant's explanation about TLS associated with Abecma:
Adverse events falling under the MedDRA PT of "Tumour lysis syndrome" were counted as TLS. Table 49 shows the characteristics of patients who had TLS after Abecma infusion in Studies MM-001 and CRB-401. In 1 patient reported in Study MM-001, TLS occurred after administration of venetoclax as a succeeding treatment. One patient reported in Study CRB-401 had a high tumor volume at baseline, but creatinine and blood urea nitrogen levels were within the reference range. Prophylactic administration of allopurinol was given from the day of Abecma infusion.

[25] An open-label, uncontrolled, global phase II study to investigate the efficacy and safety of Abecma in patients with relapsed or refractory MM and in patients with clinically high-risk MM

Table 49. List of patients with "Tumour lysis syndrome"

Clinical study	Age	Sex	Target dose	Grade	Seriousness	Causal relationship to Abecma	Time to onset (days)	Duration (days)	Outcome
Study MM-001	4[redacted]	Female	450	3	Serious	Not related	500	3	Resolved
Study CRB-401	4[redacted]	Female	450	3	Serious	Related	11	5	Resolved

PMDA's view:
Caution should be exercised against TLS in patients receiving Abecma because serious Grade 3 TLS for which a causal relationship to Abecma could not be ruled out was reported by 1 patient in Study CRB-401. Also, TLS is an event that requires attention among approved anti-CD19 CAR-expressing T cell therapies. Accordingly, the incidence of TLS in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention so that appropriate measures are taken in case of TLS.

7.R.2.2.9 Others

7.R.2.2.9.1 Secondary malignancies

The applicant's explanation about secondary malignancies:
Table 50 shows the occurrence of secondary malignancies observed in clinical studies of Abecma. Grade 4 myelodysplastic syndrome reported in 1 patient in Study CRB-401 was assessed to be causally related to Abecma by the investigator. In Study MM-001, plasmablastic lymphoma was reported in 1 patient after the retreatment with Abecma. This event was Grade 4 and occurred on Day 110 after the retreatment (Day 250 after the initial dose). The investigator assessed that the event was causally related to Abecma.

No T-cell-derived secondary malignancy has been reported to date in the clinical studies of Abecma.

In Study MM-001, the tumor tissue and the blood sample were collected from patients who experienced secondary malignancies in order to evaluate the transduced CAR gene, test for RCL, and analyze the vector insertion site. In Study CRB-401, the tumor tissue and the blood sample were collected in order to evaluate the transduced CAR gene and test for RCL. Before the data cutoff point (December 21, 2020, in Study MM-001; April 7, 2020, in Study CRB-401), 6 samples were collected from a total of 5 patients from Studies MM-001 and CRB-401 and tested for RCL. Results showed that all samples were negative for transduced CAR gene.

Table 50. List of patients with secondary malignancies

Age	Sex	Target dose	PT (MedDRA/J ver.22.0)	Grade	Seriousness	Time to onset (days)	Causal relationship to Abecma	Outcome
Study MM-001								
6[redacted]	Male	300	Basal cell carcinoma	1	Serious	338	Not related	Resolved
7[redacted]	Male	300	Lung adenocarcinoma	5	Serious	86	Not related	Dead
5[redacted]	Female	300	Anal cancer	3	Serious	77	Not related	Unresolved
5[redacted]	Female	300	Squamous cell carcinoma	2	Serious	214	Not related	Resolved
6[redacted]	Female	450	Basal cell carcinoma	1	Serious	21	Not related	Resolved
6[redacted]	Male	450	Basal cell carcinoma	2	Serious	145	Not related	Resolved
5[redacted]	Female	450	Basal cell carcinoma	2	Serious	93	Not related	Resolved
7[redacted]	Male	450	Basal cell carcinoma	2	Serious	191	Not related	Resolved
5[redacted]	Male	450	Myelodysplastic syndrome	3	Serious	363	Not related	Unresolved
5[redacted]	Male	300 (450[*1])	Plasmablastic lymphoma	4	Serious	250 (110[*2])	Related	Unresolved
Study CRB-401								
5[redacted]	Male	50	Adenocarcinoma of colon	2	Serious	81	Not related	Unresolved
6[redacted]	Female	150	Myelodysplastic syndrome	4	Serious	369	Related	Unresolved
7[redacted]	Male	150	Bowen's disease	2	Serious	200	Not related	Resolved
6[redacted]	Male	450	Bowen's disease	2	Serious	134	Not related	Resolved
6[redacted]	Male	450	Myelodysplastic syndrome	1	Serious	15	Not related	Unresolved
6[redacted]	Male	450	Malignant melanoma	1	Serious	172	Not related	Resolved
7[redacted]	Female	450	Breast cancer	2	Serious	628	Not related	Unresolved
7[redacted]	Male	450	Basal cell carcinoma	2	Serious	340	Not related	Unresolved
			Basal cell carcinoma	2	Serious	526	Not related	Resolved
			Bladder cancer	3	Serious	474	Not related	Resolved
Study MM-002								
4[redacted]	Female	300	Metastases to central nervous system	3	Serious	115	No	Resolved

*1 Target dose at retreatment
*2 Time to onset after retreatment

The incidence of the above-mentioned secondary malignancies was within the range anticipated in patients with relapsed or refractory MM (*Haematologica*. 2015;100:1340-9), and a causal relationship to Abecma was denied in many patients studied. Thus, there is no information at present that suggests any direct relationship between Abecma and secondary malignancies.

The lentiviral vector used for the manufacture of Abecma is a self-inactivating vector lacking replication competence, and it is unlikely to cause gene insertion mutation, but the risk of oncogenicity cannot be completely denied theoretically at present. Accordingly, relevant information will be continuously collected in the post-marketing setting.

PMDA's view:
A causal relationship of secondary malignancies to primary disease or prior chemotherapy cannot be ruled out, and the relationship of secondary malignancies to Abecma remains unclear at present. However, given that a causal relationship to Abecma cannot be ruled out for some of the events, caution should be exercised against secondary malignancies, and relevant information should be continuously collected in the post-marketing setting.

7.R.3 Clinical positioning and indication or performance

The proposed "Indication or Performance" of Abecma was "Relapsed or refractory multiple myeloma. Abecma should be used only in patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody."

The “Precautions Concerning Indication or Performance” included the following statements: Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with prior treatment, etc. of patients enrolled in the clinical studies described in the “Clinical Studies” section.

PMDA’s view:
On the basis of reviews in Sections “7.R.1 Efficacy,” “7.R.2 Safety,” and the review presented below, the “Indication or Performance” section should be specified as shown below. The proposed PRECAUTIONS CONCERNING INDICATION OR PERFORMANCE is acceptable.

Indication or Performance (Underline denotes additions or changes. Strikethrough denotes deletions.)
Relapsed or refractory multiple myeloma
Abecma should be used only in patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy.

Precautions Concerning Indication or Performance
Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with prior treatment, etc. of patients enrolled in the clinical studies described in the “Clinical Studies” section.

7.R.3.1 Clinical positioning and target population of Abecma

The applicant’s explanation about the clinical positioning and “Indication or Performance” of Abecma:
The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma (NCCN Guidelines) (v.4.2021) recommends triple therapy in patients with relapsed or refractory MM as a feasible standard therapy. The recommended treatment options usually include a combination of dexamethasone with 2 or more drugs with various mechanisms of actions (e.g., immunomodulatory agent, proteasome inhibitor, monoclonal antibody, histone deacetylation inhibitor, and alkylating agent). For patients with relapsed or refractory MM unable to start the triple therapy immediately, the Guidelines proposes an option of adding the third drug when the patient’s condition has improved after the dual therapy. However, the Guidelines do not clarify the priority order for the subsequent combination therapy or the best treatment method for patients who have experienced multiple relapses. Since almost all patients receive the initial treatment including an immunomodulatory agent or a proteasome inhibitor, the option for the subsequent treatment is limited if the disease has become refractory to these drugs. In patients with relapsed or refractory MM, particularly in patients with a prior treatment with multiple anti-myeloma drugs, patients with a prior treatment with an anti-CD38 antibody, and patients refractory to major anti-myeloma drugs, their response rate to treatment is low, with a short DOR and survival period (*N Engl J Med.* 2019;381:727-38, *Lancet Oncol.* 2020;21:207-21, *Clin Lymphoma Myeloma Leuk.* 2020;20:1-7).

Thus, there are urgent unmet needs for treatment options to improve the prognosis of patients with relapsed or refractory MM with at least 3 prior lines of treatments including an immunomodulatory

agent, a proteasome inhibitor, and an anti-CD38 antibody. Since results of Studies MM-001 and CRB-401 confirmed the efficacy and safety of Abecma in patients with relapsed or refractory MM with at least 3 prior lines of treatment, Abecma is considered to qualify as a new treatment option in patients afflicted with this disease.

PMDA asked the applicant to explain whether the efficacy and safety of Abecma vary depending on the number of the prior treatments in patients for whom Abecma is recommended.

The applicant's explanation:
In Study MM-001, the overall response rate in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6 anti-BCMA CAR-expressing T cells, by the number of the regimens of the prior treatment (3, 4, and ≥5), was 76.5% in 17 patients with 3 prior treatment regimens, 68.2% in 22 patients with 4 prior treatment regimens, and 75.5% in 98 patients with ≥5 prior treatment regimens, showing no tendency of a significant difference among patients with a different number of prior treatment regimens. In Japanese patients in Study MM-001, the best response was: sCR in 2 patients with 3 prior treatment regimens; VGPR in 1 patient and PR in 2 patients among 3 patients with 4 prior treatment regimens; and sCR in 2 patients, VGPR in 1 patient, and SD in 1 patient among 4 patients with ≥5 prior treatment regimens. In Study CRB-401, the overall response rate in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6 anti-BCMA CAR-expressing T cells, by the number of the regimens of the prior treatment (3, 4, and ≥5), was 100% in 6 patients with 3 prior treatment regimens, 60.0% in 10 patients with 4 prior treatment regimens, and 75.0% in 40 patients with ≥5 prior treatment regimens. Thus, both Studies MM-001 and CRB-401 demonstrated the efficacy of Abecma regardless of the number of the prior treatment regimens.

Tables 51 and 52 show the incidence of adverse events in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6 cells in Studies MM-001 and CRB-401, by the number of the prior treatment regimens (3, 4, and ≥5). Results show no clear difference or any specific tendency in the safety profile of Abecma among patients receiving a different number of prior treatment regimens although rigorous comparison is difficult because of the uneven distribution of patients with a different number of prior treatment regimens.

Table 51. Summary of safety in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6, by the number of the prior treatment regimens (3, 4, and ≥5) (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

	Number of patients (%)		
	3 prior treatment regimens N = 17 (including 2 Japanese patients)	4 prior treatment regimens N = 22 (including 3 Japanese patients)	≥5 prior treatment regimens N = 98 (including 4 Japanese patients)
All adverse events	17 (100)	22 (100)	98 (100)
Grade ≥3 adverse events	17 (100)	22 (100)	97 (99.0)
Serious adverse events	8 (47.1)	14 (63.6)	72 (73.5)
Adverse events leading to death	5 (29.4)	6 (27.3)	24 (24.5)
CRS	15 (88.2)	18 (81.8)	83 (84.7)
Cytopenia - all	17 (100)	21 (95.5)	95 (96.9)
Cytopenia - Anaemia	11 (64.7)	14 (63.6)	70 (71.4)
Cytopenia - Lymphopenia	9 (52.9)	10 (45.5)	27 (27.6)
Cytopenia - Neutropenia	17 (100)	21 (95.5)	92 (93.9)
Cytopenia - Thrombocytopenia	12 (70.6)	8 (36.4)	71 (72.4)
Neurologic toxicity	9 (52.9)	9 (40.9)	73 (74.5)

Table 52. Summary of safety in patients receiving Abecma at the target dose of 150×10^6 to 450×10^6 cells, by the number of the prior treatment regimens (3, 4, and ≥5) (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

	Number of patients (%)		
	3 prior treatment regimens N = 6	4 prior treatment regimens N = 10	≥5 prior treatment regimens N = 40
All adverse events	6 (100)	10 (100)	40 (100)
Grade ≥3 adverse events	5 (83.3)	10 (100)	40 (100)
Serious adverse events	4 (66.7)	7 (70.0)	31 (77.5)
Adverse events leading to death	1 (16.7)	1 (10.0)	5 (12.5)
CRS	6 (100)	8 (80.0)	28 (70.0)
Cytopenia - all	5 (83.3)	10 (100)	37 (92.5)
Cytopenia - Anaemia	5 (83.3)	10 (100)	26 (65.0)
Cytopenia - Lymphopenia	4 (66.7)	3 (30.0)	17 (42.5)
Cytopenia - Neutropenia	5 (83.3)	10 (100)	37 (92.5)
Cytopenia - Thrombocytopenia	4 (66.7)	7 (70.0)	31 (77.5)
Neurologic toxicity	5 (83.3)	6 (60.0)	32 (80.0)

PMDA's view:

It is generally acceptable to determine the "Indication or Performance" based on the results of Studies MM-001 and CRB-401. However, the "Indication or Performance" section should clearly state that the patient should have ≥3 prior lines of treatment histories including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. In addition to the above, Abecma is intended for patients who showed disease progression or relapse after the last prior treatment, taking account of the requirement on the last prior treatment in clinical studies.

In addition, the "Precautions Concerning Indication or Performance" section should state that "Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with the prior treatment, etc. of patients enrolled in the clinical studies described in the 'Clinical Studies' section," and that the proposed "Precautions Concerning Indication or Performance" is acceptable.

7.R.3.2 Necessity of confirming BCMA before administration of Abecma

PMDA asked the applicant to explain the necessity of confirming BCMA expression before Abecma administration.

The applicant's response:

It is considered unnecessary to confirm the expression of BCMA on tumor cells before Abecma administration, for the following reasons:

- In Study MM-001, the percentage of BCMA-expressing cells in CD138-positive myeloma cells in the bone marrow samples was analyzed in a retrospective manner. Results confirmed BCMA expression in myeloma cells (≥5%[26)]) in almost all evaluable patients (98% [110 of 112] of non-Japanese patients, 100% [6 of 6] of Japanese patients). The results are similar to those reported in the literature *(J Clin Invest.* 2019;129:2210-21, *Cancer Cell*. 2017;31:396-410, *Leuk Res.* 2018;71:106-11), suggesting that the percentage of patients without BCMA-expressing tumor cells is extremely low.
- In Study MM-001, 2 of 3 patients with a low BCMA-expression level (<50%) showed PR or better response,[27)] and in 19 patients (including 3 Japanese patients) with unknown BCMA expression on tumor cells,[28)] the overall response rate [95% CI] (%) was 78.9 [54.4, 93.9] and the rate of CR or better [95% CI] (%) was 36.8 [16.3, 61.6], showing similar efficacy results as in the entire population. The safety in this population was not significantly different from that in the entire population, either.
- CAR-expressing T cells transduced with BCMA CAR gene identical to that of Abecma have cytotoxic activity against low BCMA-expressing tumor cell lines (*Hum Gene Ther.* 2018;29:585-601).
- There is no clinically validated method for evaluating BCMA-expressing level on tumor cells currently, and assessed measurements on the expression level vary depending on the technique and sensitivity (*Leukemia.* 2020;34:985-1005). In 2 patients with a BCMA expression level of <5% in Study MM-001, the percentage of plasma cells in the bone marrow biopsy sample was extremely low, suggesting that the low expression level was due to the localization of myeloma in the bone marrow and/or the non-uniform sampling sites. Thus, it is expected that, in clinical practice as well, there are patients from whom test samples cannot be withdrawn in an appropriate manner. Given the difficulty of appropriate sampling for evaluating BCMA expression level and the effect of the testing method on the results of evaluation, there is a concern that conducting the test for BCMA expression may exclude patients who benefit from treatment with Abecma.

PMDA's view:

The applicant's above explanation is understandable. BCMA is consistently expressed on tumor cells of patients with relapsed or refractory MM. The efficacy of Abecma is expected regardless of the assessment of BCMA expression level. It is thus unnecessary to confirm BCMA expression before Abecma administration.

[26)] A majority of non-Japanese patients (101 of 112 patients) showed ≥90% BCMA expression. All 6 Japanese patients showed ≥50% BCMA expression.

[27)] PR was observed in a patient with 40% BCMA expression. sCR was observed in a patient with 1% BCMA expression.

[28)] A bone marrow sample for BCMA expression test was unavailable or CD138-positive cells were undetectable in the bone marrow sample.

7.R.4 Dosage and administration or method of use

The proposed DOSAGE AND ADMINISTRATION OR METHOD OF USE of Abecma was as follows:

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

6. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected.
7. Transportation of leukapheresis material
   The leukapheresis material is packed and transported under refrigerated conditions to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

8. Receipt and keeping of Abecma
   Abecma is received in a frozen condition and cryopreserved until immediately before use.
9. Treatment before Abecma administration
   Administer a lymphodepleting chemotherapy regimen.
   1) Administer cyclophosphamide (anhydrate) 300 mg/m^2 and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
   2) Abecma is infused 3 days after the completion of lymphodepleting chemotherapy.
10. Infusion of Abecma
    Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 150 × 10^6-450 × 10^6 cells) of CAR-expressing T cells (irrespective of body weight), administered intravenously as a single dose. Refer to the Release for Infusion Certificate for the actual cell count and dose.

The PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE section had specified the following.

Refer to the manufacturer's manual for details on the steps from the collection of cells from the patient through the administration of Abecma.

If any of the following conditions is observed in the patient, postpone the procedures such as lymphodepleting chemotherapy or Abecma administration until recovery. The administration may be postponed up to 7 days from 3 days after the completion of the lymphodepleting chemotherapy.

- Persisting serious adverse events (lung disorder, cardiac disorder, hypotension, etc.) caused by the preceding chemotherapy
- Active infection and inflammatory disease
- Active graft versus host disease (GVHD)

Premedication and preparation for Abecma administration

1. Confirm the scheduled infusion timing in advance, and adjust the time to start thawing Abecma so that infusion can be started as soon as the patient is ready.
2. In order to minimize the risk of injection reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker approximately 30 to 60 minutes before the infusion of

Abecma. Prophylactic use of systemic corticosteroids is prohibited as the use may interfere with the activity of Abecma.

3. Before thawing Abecma, confirm that the patient identity matches the information on the metal cassette and the infusion bag.
4. If the patient identity does not match the information on the metal cassette or the infusion bag, do not remove the infusion bag from the metal cassette, and notify the marketing authorization holder.
5. After confirming that the patient identity matches the information on the metal cassette and the infusion bag, remove the Abecma infusion bag from the metal cassette.
6. Before thawing Abecma, inspect the infusion bag for any damage or leaks on the infusion bag. In case any damage or leakage is noticed, do not use Abecma. Instead, notify the marketing authorization holder.
7. Transfer the infusion bag from the metal cassette to the thawing bag according to the procedure of each medical institution.
8. Abecma is supplied as one or more infusion bags containing CAR-expressing T cell suspension. If 2 or more bags are used, do not start thawing of the second and subsequent infusion bags until administration of Abecma in the first infusion bag is completed.
9. Thaw Abecma in the infusion bag completely in a thermostat bath or a dry thawing device, etc., at approximately 37°C. If clumps of cellular material are visible, swirl the infusion bag slowly. After thawing is completed, remove the infusion bag promptly from the bath. Do not wash, spin down, or resuspend cells in a new culture medium before infusion.

Administration of Abecma

10. Do not use a leukodepleting filter for Abecma infusion.
11. Ensure that ≥2 doses of tocilizumab (genetical recombination) and emergency treatment equipment are available before the infusion and during the recovery period.
12. Central venous access may be used for the infusion of Abecma and is recommended in patients with poor peripheral access.
13. Prior to infusion, confirm that the patient's identity matches the patient identifiers on the Abecma infusion bag.
14. Prime the tubing with physiological saline before Abecma infusion.
15. Complete infusion within 1 hour after the start of thawing Abecma.
16. After the entire content of the infusion bag is infused, rinse the infusion bag and the tubing with physiological saline to ensure all product is delivered.
17. If more than one infusion bags have been received, administer all bags as directed on the Release for Infusion Certificate.
18. Follow the same procedure for the second and subsequent infusion bags.
19. Abecma contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. Abecma should be disposed of as infectious waste in accordance with the universal precautions and local biosafety guidelines.

Monitoring

20. Monitor patients at least once a day for ≥1 week following infusion at appropriate medical facility for possible signs or symptoms associated with CRS or neurotoxicity.

21. Instruct patients to consult with an appropriate medical facility if any symptom is observed within 4 weeks after infusion.

PMDA's view:
On the basis of the reviews in Sections "7.R.1 Efficacy" and "7.R.2 Safety" as well as the review presented below, the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections of Abecma should be modified as follows:

Dosage and Administration or Method of Use (Underline denotes additions. Strikethrough denotes deletions.)

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material.
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported ~~under refrigerated conditions~~ to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and ~~keeping~~ storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   ~~1)~~ Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days~~.~~ and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
   ~~2) Abecma is infused 3 days after the completion of lymphodepleting chemotherapy.~~
5. Infusion of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280~~150~~ × 10^6-540 × 10^6 cells) of ~~chimeric antigen receptor (~~CAR~~)~~-expressing T cells, ~~(~~irrespective of body weight~~)~~, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min.~~ Refer to the Release for Infusion Certificate for the actual cell count and dose.~~ Retreatment with Abecma is not allowed.

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions or changes. Strikethrough denotes deletions.)

Refer to the manufacturer's manual for details on the steps from the collection of cells from the patient through the administration of Abecma.

If any of the following conditions is observed in the patient, postpone ~~a series of the procedures such as~~ lymphodepleting chemotherapy or Abecma infusion until recovery. ~~Abecma administration may be postponed up to 7 days from 3 days after the completion of the lymphodepleting chemotherapy~~.

- Persisting serious adverse events (lung disorder, cardiac disorder, hypotension, etc.) caused by the preceding chemotherapy
- Active infection and inflammatory disease
- Active graft versus host disease (GVHD)

Pretreatment

In order to facilitate the engraftment of transplanted cells, Abecma infusion should be preceded by administration of chemotherapeutic agents with a cytocidal effect such as DNA synthesis inhibitory activity or immunosuppressive activity associated with a decrease in lymphocyte count. See the "Clinical Studies" section for the details of the pretreatment given in the clinical studies.

~~Premedication and preparation for~~ Administration of Abecma

1. Confirm the scheduled infusion timing in advance and adjust the time to start thawing Abecma so that infusion can be started as soon as the patient is ready.
2. In order to minimize the risk of ~~injection reaction~~ infusion reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker approximately 30 to 60 minutes before the infusion of Abecma. Do not use corticosteroids unless a life-threatening emergency arises. Be prepared for emergency treatment of a severe event such as anaphylaxis following Abecma infusion. ~~Prophylactic use of systemic corticosteroids is prohibited as the use may interfere with the activity of Abecma.~~
3. ~~Before thawing Abecma, confirm that the patient identity matches the information on the metal cassette and the infusion bag.~~
4. ~~If the patient identity does not match the information on the metal cassette or the infusion bag, do not remove the infusion bag from the metal cassette, and notify the marketing authorization holder.~~
5. ~~After confirming that the patient identity matches the information on the metal cassette and the infusion bag, remove the Abecma infusion bag from the metal cassette.~~
6. Ensure that tocilizumab (genetical recombination) is available for prompt use in case of emergency with cytokine release syndrome.
7. Before thawing Abecma, confirm that the patient identity matches the information on the metal cassette and the infusion bag. Then remove the infusion bag from the metal cassette.
8. Do not use Abecma if any damage or leaks are noticed on the infusion bag. ~~Before thawing Abecma, inspect the infusion bag for any damage or leaks on the infusion bag. In case any damage or leakage is noticed, do not use Abecma. Instead, notify the marketing authorization holder.~~
9. ~~Transfer the infusion bag from the metal cassette to the thawing bag according to the procedure of each medical institution.~~
10. Abecma is supplied as one or more infusion bags containing CAR-expressing T cell suspension. If 2 or more bags are used, do not start thawing of the second and subsequent infusion bags until administration of Abecma in the first infusion bag is completed.
11. Thaw Abecma in the infusion bag completely in a thermostat bath or a dry thawing device, etc., at approximately 37°C. If clumps of cellular material are visible, swirl the infusion bag slowly. Do not refreeze the thawed Abecma. After thawing is completed, remove the infusion bag promptly from the bath. Do not wash, spin down, or resuspend cells in a new culture medium before infusion.

~~Administration of Abecma~~

12. Do not irradiate Abecma. Do not use a leukodepleting filter for Abecma infusion.
13. ~~Ensure that ≥2 doses of tocilizumab (genetical recombination) and emergency treatment equipment are available before the infusion and during the recovery period.~~
14. ~~Central venous access may be used for the infusion of Abecma and is recommended in patients with poor peripheral access.~~
15. Prior to infusion, confirm that the patient's identity matches the patient identifiers on the Abecma infusion bag.
16. Prime the tubing with physiological saline before Abecma infusion. After the entire content of the infusion bag is infused, rinse the infusion bag with physiological saline by backpriming to ensure delivery of as many cells as possible.
17. Complete infusion within 1 hour after the start of thawing Abecma.
18. ~~After the entire content of the infusion bag is infused, rinse the infusion bag and the tubing with physiological saline to ensure all product is delivered.~~
19. If more than one infusion bags have been received, administer all bags as directed on the Release for Infusion Certificate. Follow the same procedure as in the first infusion bag above for the second and subsequent infusion bags.
20. Abecma contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. The residual Abecma suspension should be disposed of as infectious waste in accordance with ~~the universal precautions and~~ local biosafety guidelines.

~~Monitoring~~

21. ~~Monitor patients at least once a day for ≥1 week following infusion at appropriate medical facility for possible signs or symptoms associated with CRS or neurotoxicity.~~
22. ~~Instruct patients to consult with an appropriate medical facility if any symptom is observed within 4 weeks after infusion.~~

7.R.4.1 Dosage regimen of LD chemotherapy

The applicant's explanation about the rationale for the proposed dosage regimen of LD chemotherapy:

Dosage regimen of LD chemotherapy

The rationale for the proposed dosage regimen of LD chemotherapy is as follows:

- In a clinical study in patients with non-Hodgkin lymphoma (NHL), patients receiving anti-CD19 CAR-expressing T cells after LD chemotherapy with cyclophosphamide + fludarabine showed more favorable results in terms of the growth and persistence of anti-CD19 CAR-expressing T cells and its anti-tumor effect than in those receiving anti-CD19 CAR-expressing T cells after LD chemotherapy with cyclophosphamide alone (*Sci Transl Med.* 2016;8:355ra116), suggesting the benefit of the LD chemotherapy with cyclophosphamide + fludarabine before the treatment with anti-CD19 CAR-expressing T cells. Further, in another clinical study in patients with diffuse large B-cell lymphoma (DLBCL), an antitumor effect was observed in patients who received anti-CD19 CAR-expressing T cells after administration of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 for 3 days. A transient neurologic toxicity was observed, but neither severe cardiotoxicity nor neurologic toxicity was detected (*Blood*. 2014;124:550).

- Studies MM-001 and CRB-401 confirmed the efficacy and safety of Abecma in patients with relapsed or refractory MM (including Japanese patients) when it is administered after administration of LD chemotherapy consisting of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 for 3 days.

Use of LD chemotherapy
In Studies MM-001 and CRB-401, LD chemotherapy was allowed in patients who had intact bone marrow, liver, and kidney function, and had no active infection. Also, the effect of prior treatment (including a bridging therapy) had to be washed out. In 1 patient who received Abecma at the target dose of 450 × 10^6 cells in Study CRB-401, fludarabine was not administered because of decreased kidney function, but LD chemotherapy was given to all patients who received Abecma in both Study MM-001 and Study CRB-401.

PMDA's view:
The applicant's explanation about the dosage regimen of LD chemotherapy is understandable.

LD chemotherapy, which aims to facilitate the engraftment of Abecma in the body, should be performed according to the patient's condition pre-assessed by blood test, etc., and that should be clearly mentioned in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section, considering that some patients intended for Abecma may need to undergo anticancer therapy (bridging therapy) for disease control during the Abecma manufacturing period after leukapheresis.

7.R.4.2 Dosage and administration of Abecma

The applicant's explanation about justification for the dosage regimen of Abecma:
On the basis of the results of Studies CRB-401 and MM-001 as shown below, the dosage and administration or method of use of Abecma was determined to be "The usual adult dosage is the target dose of 450 × 10^6 cells (range, 150 × 10^6-540 × 10^6 cells) of CAR-expressing T cells (irrespective of body weight), administered intravenously as a single dose."

- The recommended dose in Part B (dose expansion period) was determined to be 150 × 10^6 to 450 × 10^6 cells from the result of Part A (dose escalation period) in Study CRB-401.
- In Study MM-001 which was conducted at the target dose of 150 × 10^6 to 450 × 10^6 cells (acceptable upper limit of the actual dose: 540 × 10^6 cells) based on the data of Study CRB-401, the overall response rate in the entire population receiving Abecma (including Japanese patients) was 74.5% and the rate of CR or better was 34.3%, showing a favorable efficacy result (data cutoff on December 21, 2020). Results obtained with the target dose of 450 × 10^6 cells were the most favorable.
- The safety was generally manageable, with the safety profile being similar among different target doses except that the incidence of CRS increased in a dose-dependent manner.

The lower limit of CAR-expressing T cell count to be administered
The lower limit of CAR-expressing T cell count to be administered was determined to be 150 × 10^6 cells for the following reasons:

- In Studies MM-001 and CRB-401, the safety profile of Abecma was manageable in patients receiving the target dose of 150 × 10^6 cells.

- In Studies MM-001 and CRB-401, Abecma at the target dose of 150×10^6 cells also showed favorable efficacy when compared with those of existing therapies, as shown below:
  - A pooled analysis of 22 patients receiving the target dose of 150×10^6 cells in Study MM-001 or CRB-401 showed the overall response rate of 54.5%, the rate of VGPR or better of 40.9%, the rate of CR or better of 31.8%, and the median DOR of 10.8 months (data cutoff on April 7, 2020), indicating a clinically significant persistent effect.
  - The efficacy observed in the above 22 patients was compared with the efficacy observed in the MAMMOTH Study (*Leukemia.* 2019;33:2266-75) in patients with relapsed or refractory MM previously treated with an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody or in Study NDS-MM-003, which collected real-world data. The results tended to favor Abecma at the target dose of 150×10^6 cells for the overall response rate, rate of VGPR or better, rate of CR or better, and median DOR, although there are limitations to the comparison with the external control.
- In the Japanese patients, only the target dose of 450×10^6 cells was investigated. However, the efficacy, safety, and pharmacokinetics at this target dose were similar between Japanese and non-Japanese patients, suggesting similar efficacy and safety profiles between the two populations at 150×10^6 cells.

The upper limit of CAR-expressing T cell count to be administered

The upper limit of CAR-expressing T cell count to be administered was determined to be 540×10^6 for the following reasons:

- In Studies CRB-401 and MM-001, Abecma was administered at the dose range not exceeding by 20% the target dose specified in the study protocol (upper limit, 540×10^6 CAR-expressing T cells). The maximum dose actually administered was 523.64×10^6 cells (Japanese patient in Study MM-001).
- In Study MM-001 (data cutoff on December 21, 2020) and Study CRB-401 (data cutoff on April 7, 2020), occurrences of adverse events in patients receiving the target dose of 450×10^6 cells were investigated by subgroups ($\leq 450 \times 10^6$ cells, $>450 \times 10^6$ cells to $\leq 500 \times 10^6$ cells, $>500 \times 10^6$ cells) classified by the actual dose (450×10^6 cells ± 20%). Tables 53 and 54 show the results. No clear difference or any consistent tendency was observed in the safety profile among groups receiving different actual dose, although rigorous comparison is difficult due to an imbalance in the number of patients in the subgroups.

Table 53. Summary of safety by actual dose subgroup in patients receiving the target dose of 450×10^6 cells (Study MM-001, Abecma cohort, data cutoff on December 21, 2020)

	Number of patients (%)		
	≤450 × 10^6 cells N = 4 (including 1 Japanese patient)	>450 × 10^6-≤500 × 10^6 cells N = 53 (including 6 Japanese patients)	>500 × 10^6 cells N = 6 (including 2 Japanese patients)
All adverse events	4 (100)	53 (100)	6 (100)
Grade ≥3 adverse events	4 (100)	53 (100)	6 (100)
Serious adverse events	3 (75.0)	36 (67.9)	5 (83.3)
Adverse events leading to death	2 (50.0)	12 (22.6)	1 (16.7)
CRS	4 (100)	51 (96.2)	6 (100)
Cytopenia - All	4 (100)	52 (98.1)	6 (100)
Cytopenia - Anaemia	4 (100)	31 (58.5)	5 (83.3)
Cytopenia - Lymphopenia	2 (50.0)	19 (35.8)	3 (50.0)
Cytopenia - Neutropenia	4 (100)	50 (94.3)	6 (100)
Cytopenia - Thrombocytopenia	4 (100)	33 (62.3)	5 (83.3)
Neurologic toxicity	1 (25.0)	30 (56.6)	2 (33.3)

Table 54. Summary of safety by actual dose subgroup in patients receiving the target dose of 450×10^6 cells (Study CRB-401, Abecma cohort, data cutoff on April 7, 2020)

	Number of patients (%)		
	≤450 × 10^6 cells N = 14	>450 × 10^6-≤500 × 10^6 cells N = 24	>500 × 10^6 cells N = 0
All adverse events	14 (100)	24 (100)	0
Grade ≥3 adverse events	14 (100)	23 (95.8)	0
Serious adverse events	10 (71.4)	19 (79.2)	0
Adverse events leading to death	0	3 (12.5)	0
CRS	12 (85.7)	23 (95.8)	0
Cytopenia - All	13 (92.9)	22 (91.7)	0
Cytopenia - Anaemia	9 (64.3)	21 (87.5)	0
Cytopenia - Lymphopenia	5 (35.7)	11 (45.8)	0
Cytopenia - Neutropenia	13 (92.9)	22 (91.7)	0
Cytopenia - Thrombocytopenia	10 (71.4)	19 (79.2)	0
Neurologic toxicity	11 (78.6)	18 (75.0)	0

PMDA's view:

It is acceptable to determine the dosage regimen as "a single intravenous administration at the target dose of 450 × 10^6 CAR-expressing T cells, irrespective of body weight" based on the results of Studies CRB-401 and MM-001.

Taking the benefit/risk balance into consideration, it is also acceptable to set the upper limit of CAR-expressing T cells as 540 × 10^6 cells based on the doses in clinical studies. However, given the limited number of patients treated with >500 × 10^6 cells, information on safety should be collected continuously in the post-marketing setting.

It is inadequate to set the lower limit as 150 × 10^6 cells because only 4 patients were treated with the target dose of 150 × 10^6 cells with the efficacy at this dose remaining unclear, although they were included in Study MM-001 which confirmed the efficacy of Abecma. Given the following explanations of the applicant, PMDA concluded that the appropriate lower limit of CAR-expressing T cells should be 280 × 10^6 cells, considering that, in patients receiving the target dose of 300 × 10^6 cells in Study MM-001, the lowest actual dose of CAR-expressing T cells administered was 277.27 × 10^6 cells.

- Among patients who received the target dose of 300 × 10^6 cells in Study MM-001, data of 18 patients who received less than 300 × 10^6 CAR-expressing T cells were subjected to subgroup analysis. Results showed that the overall response rate [95% CI] (%) was 66.7 [41.0, 86.7], rate of CR or better

[95% CI] (%) was 22.2 [6.4, 47.6], median DOR [95% CI] (months) was 5.8 [2.1, 16.7], and median PFS [95% CI] (months) was 5.3 [2.9, 10.9], demonstrating a clinically significant persistent effect, without showing any clear declining trend in the efficacy of Abecma in this subgroup, although detailed analysis is difficult for reasons including the limited number of patients investigated.

7.R.4.3 Infusion speed of Abecma

PMDA asked the applicant to explain the necessity of defining Abecma infusion speed in the dosage and administration or method of use of Abecma.

The applicant's explanation:
The protocols of Studies MM-001 and CRB-401 specified that the administration of the specified volume of the cell suspension in each infusion bag should be completed within 1 hour after the start of thawing but did not specify the infusion speed; the cell suspension was allowed to drip by gravity.

For the following reasons, it is unnecessary to specify the infusion speed of Abecma. It is appropriate to infuse Abecma by gravity infusion, as was the case with the clinical studies.

- Abecma contains potassium. The package insert of potassium chloride preparation allows intravenous administration of potassium from the peripheral line at the maximum concentration of 40 mEq/L and the maximum speed of 19.2 mEq/h. In a single intravenous administration of Abecma at the maximum volume of 250 mL, the maximum amount of potassium administered is 274 mg (approximately 7 mEq, maximum concentration 28 mEq/L), which is lower than the maximum permitted concentration of potassium (40 mEq/L).
- The maximum permitted infusion speed of potassium (19.2 mEq/h) corresponds to approximately 11.4 mL/min for Abecma.[29)] In Study MM-001, of 11 patients in whom the infusion speed exceeded 11.4 mL/min with at least 1 Abecma bag, 3 of 11 patients (27.3%) experienced hyperkalaemia, an adverse event with a possible relationship to potassium administration (infused-related reaction, hyperkalaemia, or arrhythmia). However, hyperkalaemia occurred on Day 2 (1 patient, Grade 1), on Day 40 (1 patient, Grade 1), or on Day 232 (1 patient, Grade 3) after Abecma administration. A causal relationship of Abecma to the event could not be ruled out only for the event occurring on Day 2, but this event occurred neither on the day of administration nor on the next day of administration.

PMDA instructed the applicant to specify the upper limit of the infusion speed of Abecma in DOSAGE AND ADMINISTRATION OR METHOD OF USE of Abecma to avoid an abrupt increase in blood potassium concentration caused by Abecma administration, by considering the maximum permitted speed in intravenous administration specified in the package insert of potassium chloride preparation, since the possibility of hyperkalaemia associated with a high infusion speed of Abecma cannot be ruled out.

[29)] The infusion speed of 19.2 mEq/h corresponds to 0.32 mEq/min. It takes approximately 21.9 minutes to administer 7 mEq. When the maximum volume of Abecma (250 mL) is administered over approximately 21.9 minutes, the infusion speed is approximately 11.4 mL/minute.

The applicant's response:
The DOSAGE AND ADMINISTRATION OR METHOD OF USE section will require intravenous administration at a speed not exceeding 10 mL/min, by considering the maximum permitted speed in intravenous administration of potassium solution specified in the package insert of potassium chloride preparation.

PMDA accepted the applicant's response.

7.R.4.4 Monitoring after Abecma administration

PMDA asked the applicant to explain the appropriateness of the description on the monitoring after Abecma administration in the "Precautions Concerning Dosage and Administration or Method of Use" section.

The applicant's explanation:
Most of CRS and neurologic toxicity[10)] identified by the investigators in Studies MM-001 and CRB-401 occurred within 1 week after Abecma administration, indicating the importance of monitoring for CRS and neurologic toxicity for 1 week after Abecma administration. In clinical studies, patients were monitored for physical findings (including periodical neurological testing and vital sign measurements) and by blood test, every day up to Day 4 and on Day 7 in Study CRB-401 and every day up to Day 14 in Study MM-001. In both studies, CRS and neurologic toxicity were generally manageable by the detailed safety monitoring for at least 1 week after administration.

In Study MM-001, the time to the first onset of CRS and neurologic toxicity[10)] identified by the investigator was within 2 weeks after Abecma administration in all patients. In Study CRB-401, the median time (range) to the first onset of CRS following the administration of Abecma at the target dose of 150×10^6 to 450×10^6 cells was 2.0 days (1-17 days), and the median time (range) to the first onset of neurologic toxicity (narrow)[30)] was 5.0 days (1-740 days). Of 23 patients who experienced neurologic toxicity (narrow) (not including CRS symptoms), 18 patients experienced the first onset of the event within 4 weeks after Abecma administration. Accordingly, it is considered appropriate that careful safety monitoring be performed for at least 4 weeks after Abecma administration so that patients receive treatment promptly at the medical institutions as necessary.

On the basis of the above, it is considered appropriate to perform monitoring at least once a day for 1 week after Abecma administration in the post-marketing setting as in clinical studies. To deal flexibly with each patient's situation, the patient was allowed to consult other medical institution if the attending physician considers it clinically acceptable to refer the treatment and safety monitoring within 4 weeks after administration to another medical institution. In such a case, the physician who used Abecma should provide detailed information on the patient and on the characteristics of Abecma and keep in

30) Events that fall under any of the following were tabulated:
Acalculia, disturbance in attention, metabolic encephalopathy, agitation, dysarthria, motor dysfunction, amnesia, dyscalculia, myoclonus, aphasia, dysgraphia, neurotoxicity, apraxia, encephalopathy, nystagmus, asterixis, gait disturbance, perseveration, ataxia, generalised tonic-clonic seizure, postural tremor, automatism, hallucination, restlessness, bradyphrenia, visual hallucination, convulsive seizure, brain oedema, hemiparesis, sleep deprivation, cerebral haemorrhage, hypersomnia, sleep disorder, cognitive disorder, hypertonia, somnolence, coma, hypotonia, speech disorder, confusional state, insomnia, status epilepticus. delirium, lethargy, stupor, delusion, leukoencephalopathy, thinking abnormal, depressed level of consciousness, memory impairment, tremor, disorientation, mental status changes

close contact with the medical institution that takes over the treatment. Since these measures will ensure the patient's safety, the proposed monitoring method is considered appropriate.

PMDA's view:
Abecma infusion and monitoring in the outpatient setting may pose a safety concern. Adverse events such as CRS and neurologic toxicity have occurred frequently during the early phase after Abecma infusion with some serious cases. Therefore, patients should undergo Abecma infusion and precise monitoring under hospitalization [see Sections 7.R.2.2.1 and 7.R.2.2.3]. The descriptions on monitoring in the "Precautions Concerning Dosage and Administration or Method of Use" section should be deleted so that patients are properly monitored for safety after Abecma administration. Also, healthcare professionals should be provided with appropriate information and precautions, including the necessity of monitoring patients under hospitalization, via the written materials.

7.R.4.5 Retreatment with Abecma

In Studies MM-001 and CRB-401, retreatment with Abecma was permitted if PD was observed in ≥8 weeks after Abecma administration in patients with best response of SD or better to the initial dose. PMDA asked the applicant to explain whether retreatment with Abecma is recommended.

The applicant's explanation:
In Study MM-001, 31 patients were retreated with Abecma. Of the 31 patients, 29 received the target dose of 450×10^6 cells, and 2 received the target dose of 300×10^6 cells. PR or better response was observed in 6 of the 31 patients (19.4%) retreated with Abecma (VGPR in 1 patient [3.2%] and PR in 5 patients [16.1%] by investigator's assessment). Other responses were SD in 5 patients (16.1%), PD in 18 patients (58.1%), and no response data available in 2 patients. The median PFS [95% CI] (months) after the retreatment was 1.0 [1.0, 2.0]. Thus, the overall response rate after the retreatment was low, with a shorter PFS compared with the results after the initial treatment, albeit based on the limited data.

On the other hand, the safety profile was manageable. There was no Grade 3 or 4 CRS and no neurologic toxicity[10)] identified by the investigator.

In Study CRB-401, 18 patients were retreated with Abecma (8 patients in Part A, 10 patients in Part B). Efficacy and safety of retreatment were similar to those in Study MM-001.

Because of the limited data on retreatment with Abecma, it is difficult to evaluate the benefit-risk of the retreatment. Accordingly, retreatment with Abecma is not recommended. The information that the experience of retreatment with Abecma is limited and efficacy and safety have not been established will be communicated to healthcare professionals via written materials.

PMDA's view:
Retreatment with Abecma is not recommended at present because of the limited experience and the lower efficacy than the initial treatment. This is important information, and the DOSAGE AND ADMINISTRATION OR METHOD OF USE should clearly state that patients should not be retreated with Abecma.

8. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation about the post-marketing surveillance plan for Abecma:
In order to evaluate the safety, etc. of Abecma in clinical use, the applicant proposed a plan of post-marketing surveillance covering all patients with relapsed or refractory MM treated with Abecma.

The safety specifications of the surveillance include the following:
"CRS," "neurologic toxicity," "cytopenia," "hypogammaglobulinaemia," "infection," "secondary malignancies (including oncogenesis due to insertional mutagenesis caused by lentiviral vector)," "tumour lysis syndrome," and "aggravation of graft versus host disease," which are adverse events anticipated to occur in the post-marketing setting based on their occurrence in Studies MM-001 and CRB-401; and "impact on pregnancy and lactation," "long-term safety," and "safety in elderly patients" as missing information on Abecma.

The surveillance plans to cover 200 patients based on the number of patients expected to receive Abecma in the post-marketing setting (over 2 years after the market launch of Abecma) in consideration of the importance of long-term follow-up and the incidences of the events i.e., those included in the safety specifications, in Studies MM-001 and CRB-401.

The maximum of an 8-year follow-up period was specified to allow the evaluation of each specification item of the surveillance.

PMDA's view:
Because of extremely limited safety data of Abecma from Japanese patients, the applicant should conduct all-case surveillance and collect post-marketing data from all patients and provide healthcare professionals with available safety information promptly.

The safety specifications of surveillance covering all treated patients should also include "haemophagocytic lymphohistiocytosis" and "hypersensitivity," taking account of the review in Section "7.R.2. Safety."

The planned sample size and the follow-up period proposed by the applicant are acceptable.

Details of the post-marketing use-results survey will be finalized taking account of comments from the Expert Discussion on the evaluation of the safety of Abecma.

9. Adverse Events Observed in Clinical Studies

Data on death reported in the clinical studies submitted for safety evaluation are presented in Section "7.1 Evaluation data." The main adverse events other than death are shown below.

9.1 Foreign phase I study (Study CRB-401)

Adverse events were observed in all patients. Adverse events for which a causal relationship to Abecma could not be ruled out were observed in 2 of 3 patients (66.7%) at the target dose of 50×10^6 cells, in

13 of 18 patients (72.2%) at 150 × 10^6 cells, in 37 of 38 patients (97.4%) at 450 × 10^6 cells, and in 3 of 3 patients (100%) at 800 × 10^6 cells. Table 55 shows adverse events with an incidence of ≥10% at any target dose.

Table 55. Adverse events with an incidence of ≥10% at any target dose (Study CRB-401)

SOC PT (MedDRA/J ver.22.0)	Number of patients (%) 50 × 10^6 cells N = 3		150 × 10^6 cells N = 18		450 × 10^6 cells N = 38		800 × 10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	18 (100)	18 (100)	38 (100)	37 (97.4)	3 (100)	3 (100)
Blood and lymphatic system disorders								
Neutropenia	3 (100)	3 (100)	16 (88.9)	15 (83.3)	35 (92.1)	34 (89.5)	3 (100)	3 (100)
Anaemia	3 (100)	2 (66.7)	11 (61.1)	6 (33.3)	30 (78.9)	24 (63.2)	3 (100)	3 (100)
Thrombocytopenia	2 (66.7)	2 (66.7)	13 (72.2)	10 (55.6)	29 (76.3)	21 (55.3)	2 (66.7)	2 (66.7)
Leukopenia	3 (100)	3 (100)	12 (66.7)	11 (61.1)	23 (60.5)	22 (57.9)	2 (66.7)	2 (66.7)
Lymphopenia	0	0	7 (38.9)	7 (38.9)	16 (42.1)	15 (39.5)	0	0
Febrile neutropenia	0	0	3 (16.7)	2 (11.1)	6 (15.8)	5 (13.2)	1 (33.3)	1 (33.3)
Gastrointestinal disorders								
Diarrhoea	0	0	4 (22.2)	1 (5.6)	18 (47.4)	2 (5.3)	2 (66.7)	0
Nausea	0	0	6 (33.3)	0	17 (44.7)	1 (2.6)	1 (33.3)	0
Constipation	0	0	3 (16.7)	0	13 (34.2)	0	1 (33.3)	0
Vomiting	0	0	2 (11.1)	0	12 (31.6)	1 (2.6)	2 (66.7)	0
Abdominal pain	0	0	0	0	7 (18.4)	0	0	0
Dry mouth	1 (33.3)	0	2 (11.1)	0	2 (5.3)	0	0	0
Dyspepsia	0	0	3 (16.7)	0	1 (2.6)	0	1 (33.3)	0
Stomatitis	0	0	2 (11.1)	0	1 (2.6)	0	0	0
Abdominal mass	1 (33.3)	0	0	0	0	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Mouth haemorrhage	1 (33.3)	1 (33.3)	0	0	0	0	0	0
Rectal haemorrhage	1 (33.3)	0	0	0	0	0	0	0
Toothache	0	0	1 (5.6)	0	0	0	1 (33.3)	0
Immune system disorders								
CRS	2 (66.7)	0	7 (38.9)	0	35 (92.1)	3 (7.9)	3 (100)	1 (33.3)
Hypogammaglobulinaemia	0	0	4 (22.2)	0	5 (13.2)	0	0	0
General disorders and administration site conditions								
Fatigue	0	0	9 (50.0)	1 (5.6)	20 (52.6)	3 (7.9)	1 (33.3)	0
Pyrexia	2 (66.7)	0	6 (33.3)	0	15 (39.5)	1 (2.6)	1 (33.3)	0
Oedema peripheral	0	0	5 (27.8)	0	13 (34.2)	1 (2.6)	1 (33.3)	0
Chills	0	0	4 (22.2)	0	10 (26.3)	0	0	0
Asthenia	0	0	1 (5.6)	0	4 (10.5)	1 (2.6)	0	0
Pain	0	0	1 (5.6)	0	3 (7.9)	0	1 (33.3)	0
General physical health deterioration	3 (100)	3 (100)	2 (11.1)	2 (11.1)	2 (5.3)	2 (5.3)	1 (33.3)	1 (33.3)
Gait disturbance	0	0	2 (11.1)	0	1 (2.6)	0	0	0
Non-cardiac chest pain	1 (33.3)	0	0	0	1 (2.6)	0	0	0
Peripheral swelling	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Metabolism and nutrition disorders								
Hypophosphataemia	0	0	6 (33.3)	3 (16.7)	16 (42.1)	9 (23.7)	0	0
Hypokalaemia	0	0	3 (16.7)	1 (5.6)	15 (39.5)	1 (2.6)	1 (33.3)	0
Hypocalcaemia	0	0	3 (16.7)	1 (5.6)	12 (31.6)	2 (5.3)	2 (66.7)	0
Hypoalbuminaemia	1 (33.3)	0	3 (16.7)	0	11 (28.9)	0	0	0
Hyperglycaemia	0	0	1 (5.6)	0	9 (23.7)	2 (5.3)	0	0
Hyponatraemia	1 (33.3)	1 (33.3)	2 (11.1)	1 (5.6)	8 (21.1)	2 (5.3)	1 (33.3)	1 (33.3)
Hypomagnesaemia	0	0	4 (22.2)	0	7 (18.4)	0	0	0
Decreased appetite	0	0	3 (16.7)	0	6 (15.8)	0	1 (33.3)	0
Hypercalcaemia	0	0	0	0	1 (2.6)	0	1 (33.3)	0
Hyperkalaemia	0	0	2 (11.1)	0	1 (2.6)	0	0	0
Hypermagnesaemia	0	0	2 (11.1)	1 (5.6)	1 (2.6)	0	0	0
Hyperuricaemia	0	0	2 (11.1)	1 (5.6)	1 (2.6)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	2 (66.7)	0	7 (38.9)	0	17 (44.7)	0	0	0
Nasal congestion	0	0	4 (22.2)	0	10 (26.3)	0	2 (66.7)	0
Dyspnoea	1 (33.3)	0	3 (16.7)	0	6 (15.8)	0	1 (33.3)	0
Hypoxia	0	0	1 (5.6)	0	6 (15.8)	3 (7.9)	0	0
Productive cough	0	0	2 (11.1)	0	6 (15.8)	0	1 (33.3)	0
Epistaxis	0	0	1 (5.6)	0	5 (13.2)	1 (2.6)	0	0
Oropharyngeal pain	1 (33.3)	0	0	0	5 (13.2)	0	0	0
Dyspnoea exertional	0	0	2 (11.1)	0	2 (5.3)	0	0	0
Pleural effusion	0	0	0	0	2 (5.3)	0	1 (33.3)	1 (33.3)
Rhinorrhoea	0	0	0	0	2 (5.3)	0	1 (33.3)	0
Pulmonary congestion	0	0	0	0	0	0	1 (33.3)	0

SOC PT (MedDRA/J ver.22.0)	Number of patients (%) 50×10^6 cells N = 3		 150×10^6 cells N = 18		 450×10^6 cells N = 38		 800×10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections and infestations								
Upper respiratory tract infection	2 (66.7)	0	8 (44.4)	1 (5.6)	13 (34.2)	3 (7.9)	1 (33.3)	0
Urinary tract infection	0	0	2 (11.1)	0	7 (18.4)	0	0	0
Pneumonia	0	0	0	0	3 (7.9)	2 (5.3)	1 (33.3)	1 (33.3)
Respiratory syncytial virus infection	1 (33.3)	0	2 (11.1)	0	2 (5.3)	0	0	0
Lung infection	0	0	2 (11.1)	2 (11.1)	1 (2.6)	1 (2.6)	0	0
Pneumonia bacterial	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Respiratory tract infection	0	0	0	0	0	0	1 (33.3)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	0	0	6 (33.3)	0	14 (36.8)	0	0	0
Back pain	1 (33.3)	0	6 (33.3)	1 (5.6)	7 (18.4)	1 (2.6)	0	0
Musculoskeletal pain	0	0	3 (16.7)	0	5 (13.2)	0	0	0
Pain in extremity	1 (33.3)	0	0	0	5 (13.2)	0	2 (66.7)	0
Musculoskeletal discomfort	0	0	0	0	4 (10.5)	0	0	0
Myalgia	1 (33.3)	0	2 (11.1)	0	4 (10.5)	0	0	0
Musculoskeletal chest pain	0	0	3 (16.7)	1 (5.6)	3 (7.9)	0	1 (33.3)	0
Bone pain	1 (33.3)	0	2 (11.1)	0	2 (5.3)	0	1 (33.3)	0
Muscle spasms	0	0	0	0	2 (5.3)	0	1 (33.3)	0
Muscular weakness	0	0	3 (16.7)	0	1 (2.6)	0	0	0
Arthritis	1 (33.3)	0	0	0	0	0	0	0
Arthritis reactive	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Groin pain	0	0	0	0	0	0	1 (33.3)	0
Muscle twitching	0	0	0	0	0	0	1 (33.3)	0
Neck pain	0	0	2 (11.1)	0	0	0	0	0
Pain in jaw	1 (33.3)	0	0	0	0	0	0	0
Nervous system disorders								
Headache	1 (33.3)	0	5 (27.8)	0	12 (31.6)	0	0	0
Dizziness	0	0	3 (16.7)	0	8 (21.1)	1 (2.6)	2 (66.7)	0
Neurotoxicity	0	0	1 (5.6)	0	6 (15.8)	1 (2.6)	0	0
Syncope	0	0	1 (5.6)	1 (5.6)	4 (10.5)	2 (5.3)	0	0
Tremor	0	0	1 (5.6)	0	4 (10.5)	0	0	0
Paraesthesia	1 (33.3)	0	0	0	2 (5.3)	0	0	0
Neuropathy peripheral	0	0	1 (5.6)	0	0	0	1 (33.3)	0
Numb chin syndrome	1 (33.3)	0	0	0	0	0	0	0
Investigations								
Blood alkaline phosphatase increased	0	0	1 (5.6)	0	7 (18.4)	0	0	0
Transaminases increased	0	0	3 (16.7)	0	5 (13.2)	1 (2.6)	1 (33.3)	0
Weight decreased	0	0	0	0	5 (13.2)	0	0	0
Blood creatinine increased	0	0	2 (11.1)	0	4 (10.5)	0	0	0
Weight increased	0	0	0	0	4 (10.5)	0	0	0
Blood iron increased	0	0	0	0	0	0	1 (33.3)	0
Cardiac murmur	0	0	0	0	0	0	1 (33.3)	0
Vascular disorders								
Hypertension	1 (33.3)	0	2 (11.1)	1 (5.6)	8 (21.1)	5 (13.2)	0	0
Hypotension	1 (33.3)	1 (33.3)	5 (27.8)	1 (5.6)	4 (10.5)	0	0	0
Deep vein thrombosis	0	0	1 (5.6)	0	0	0	1 (33.3)	1 (33.3)
Thrombophlebitis superficial	1 (33.3)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Rash	0	0	0	0	4 (10.5)	0	0	0
Pruritus	0	0	3 (16.7)	0	3 (7.9)	0	0	0
Erythema	0	0	1 (5.6)	0	2 (5.3)	0	1 (33.3)	0
Alopecia	0	0	1 (5.6)	0	1 (2.6)	0	1 (33.3)	0
Hyperhidrosis	0	0	0	0	1 (2.6)	0	1 (33.3)	0
Pruritus generalised	1 (33.3)	0	0	0	0	0	0	0
Rash maculo-papular	1 (33.3)	0	2 (11.1)	0	0	0	1 (33.3)	0
Seborrhoeic dermatitis	0	0	0	0	0	0	1 (33.3)	0
Skin disorder	0	0	2 (11.1)	0	0	0	0	0
Swelling face	0	0	0	0	0	0	1 (33.3)	0
Cardiac disorders								
Tachycardia	0	0	2 (11.1)	0	6 (15.8)	0	1 (33.3)	0
Sinus tachycardia	1 (33.3)	0	4 (22.2)	1 (5.6)	3 (7.9)	1 (2.6)	1 (33.3)	0
Palpitations	0	0	0	0	1 (2.6)	0	1 (33.3)	0
Intracardiac mass	0	0	0	0	0	0	1 (33.3)	1 (33.3)
Pericardial effusion	0	0	1 (5.6)	1 (5.6)	0	0	1 (33.3)	1 (33.3)
Psychiatric disorders								
Insomnia	0	0	2 (11.1)	0	5 (13.2)	0	1 (33.3)	0
Depression	0	0	1 (5.6)	0	1 (2.6)	0	1 (33.3)	0
Injury, poisoning and procedural complications								
Femur fracture	0	0	0	0	1 (2.6)	1 (2.6)	1 (33.3)	1 (33.3)
Arthropod bite	0	0	2 (11.1)	0	0	0	0	0
Procedural pain	0	0	2 (11.1)	0	0	0	0	0

SOC PT (MedDRA/J ver.22.0)	Number of patients (%) 50×10^6 cells N = 3		150×10^6 cells N = 18		450×10^6 cells N = 38		800×10^6 cells N = 3	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders								
Vision blurred	0	0	0	0	2 (5.3)	0	1 (33.3)	0
Lacrimation increased	0	0	3 (16.7)	0	1 (2.6)	0	0	0
Renal and urinary disorders								
Proteinuria	1 (33.3)	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Adenocarcinoma of colon	1 (33.3)	0	0	0	0	0	0	0
Ear and labyrinth disorders								
Ear pain	0	0	2 (11.1)	0	2 (5.3)	0	0	0
Deafness	0	0	1 (5.6)	0	0	0	1 (33.3)	0
Tympanic membrane perforation	0	0	0	0	0	0	1 (33.3)	0
Reproductive system and breast disorders								
Pelvic pain	0	0	0	0	0	0	1 (33.3)	0

Serious adverse events were observed in 3 of 3 patients (100%) at the target dose of 50×10^6 cells, in 13 of 18 patients (72.2%) at 150×10^6 cells, in 29 of 38 patients (76.3%) at 450×10^6 cells, and in 3 of 3 patients (100%) at 800×10^6 cells. Serious adverse events observed in ≥2 patients at any target dose were general physical health deterioration in 3 patients (100%) at the target dose of 50×10^6 cells; CRS in 3 patients (16.7%), lung infection, pyrexia, general physical health deterioration, and neutropenia in 2 patients (11.1%) each at 150×10^6 cells; CRS in 7 patients (18.4%), pyrexia in 4 patients (10.5%), upper respiratory tract infection, general physical health deterioration, and febrile neutropenia in 2 patients (5.3%) each at 450×10^6 cells; and CRS in 2 patients (66.7%) at 800×10^6 cells. A causal relationship to Abecma could not be ruled out for CRS in 3 patients, lung infection in 2 patients, pyrexia and neutropenia in 1 patient each at the target dose of 150×10^6 cells; CRS in 7 patients, pyrexia and febrile neutropenia in 1 patient each at 450×10^6 cells; and CRS in 2 patients at 800×10^6 cells.

9.2 Global phase II study (Study MM-001)

Adverse events were observed in all patients. Adverse events for which a causal relationship to Abecma could not be ruled out were observed in 4 of 4 patients (100%) at the target dose of 150×10^6 cells, in 67 of 70 patients (95.7%) at 300×10^6 cells, and in 63 of 63 patients (100%) at 450×10^6 cells. Table 56 shows adverse events with an incidence of ≥10% at any target dose.

Table 56. Adverse events with an incidence of ≥10% at any target dose (Study MM-001)

SOC PT (MedDRA/J ver.22.0)	Number of patients (%) 150×10^6 cells N = 4		300×10^6 cells N = 70		450×10^6 cells N = 63	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	4 (100)	70 (100)	69 (98.6)	63 (100)	63 (100)
Blood and lymphatic system disorders						
Neutropenia	4 (100)	4 (100)	62 (88.6)	59 (84.3)	60 (95.2)	60 (95.2)
Thrombocytopenia	4 (100)	3 (75.0)	42 (60.0)	34 (48.6)	42 (66.7)	36 (57.1)
Anaemia	4 (100)	4 (100)	51 (72.9)	42 (60.0)	40 (63.5)	37 (58.7)
Leukopenia	2 (50.0)	2 (50.0)	34 (48.6)	30 (42.9)	26 (41.3)	26 (41.3)
Lymphopenia	2 (50.0)	2 (50.0)	19 (27.1)	19 (27.1)	22 (34.9)	21 (33.3)
Febrile neutropenia	2 (50.0)	2 (50.0)	11 (15.7)	11 (15.7)	9 (14.3)	8 (12.7)
Immune system disorders						
CRS	2 (50.0)	0	53 (75.7)	4 (5.7)	61 (96.8)	3 (4.8)
Hypogammaglobulinaemia	1 (25.0)	0	15 (21.4)	0	15 (23.8)	2 (3.2)
Metabolism and nutrition disorders						
Hypokalaemia	1 (25.0)	0	28 (40.0)	1 (1.4)	19 (30.2)	2 (3.2)
Hypophosphataemia	0	0	24 (34.3)	12 (17.1)	19 (30.2)	13 (20.6)
Decreased appetite	1 (25.0)	0	17 (24.3)	0	12 (19.0)	2 (3.2)
Hypocalcaemia	0	0	22 (31.4)	5 (7.1)	12 (19.0)	5 (7.9)

SOC PT (MedDRA/J ver.22.0)	Number of patients (%) 150 × 10^6 cells N = 4 All Grades	 Grade ≥3	 300 × 10^6 cells N = 70 All Grades	 Grade ≥3	 450 × 10^6 cells N = 63 All Grades	 Grade ≥3
Hypomagnesaemia	1 (25.0)	0	20 (28.6)	0	9 (14.3)	0
Hyponatraemia	1 (25.0)	0	15 (21.4)	5 (7.1)	9 (14.3)	3 (4.8)
Hypoalbuminaemia	2 (50.0)	0	12 (17.1)	3 (4.3)	8 (12.7)	1 (1.6)
Hypercalcaemia	1 (25.0)	0	4 (5.7)	0	4 (6.3)	0
Gastrointestinal disorders						
Diarrhoea	2 (50.0)	0	23 (32.9)	1 (1.4)	21 (33.3)	2 (3.2)
Nausea	1 (25.0)	0	20 (28.6)	0	16 (25.4)	0
Vomiting	0	0	11 (15.7)	0	10 (15.9)	0
Constipation	0	0	14 (20.0)	0	8 (12.7)	0
Dyspepsia	0	0	7 (10.0)	0	2 (3.2)	0
Oral mucosal erythema	1 (25.0)	0	0	0	0	0
Infections and infestations						
Influenza	1 (25.0)	0	2 (2.9)	0	9 (14.3)	4 (6.3)
Pneumonia	0	0	8 (11.4)	4 (5.7)	8 (12.7)	5 (7.9)
Upper respiratory tract infection	0	0	13 (18.6)	0	7 (11.1)	1 (1.6)
Rhinovirus infection	1 (25.0)	1 (25.0)	4 (5.7)	0	1 (1.6)	0
Sinusitis	1 (25.0)	0	5 (7.1)	0	1 (1.6)	0
Arthritis infective	1 (25.0)	1 (25.0)	0	0	0	0
Enterovirus infection	1 (25.0)	0	0	0	0	0
General disorders and administration site conditions						
Fatigue	1 (25.0)	0	29 (41.4)	2 (2.9)	14 (22.2)	1 (1.6)
Pyrexia	0	0	18 (25.7)	2 (2.9)	14 (22.2)	1 (1.6)
Asthenia	0	0	7 (10.0)	0	10 (15.9)	2 (3.2)
General physical health deterioration	1 (25.0)	1 (25.0)	15 (21.4)	14 (20.0)	7 (11.1)	7 (11.1)
Oedema peripheral	1 (25.0)	0	12 (17.1)	0	6 (9.5)	0
Chills	1 (25.0)	0	10 (14.3)	0	3 (4.8)	0
Pain	2 (50.0)	0	3 (4.3)	0	2 (3.2)	0
Chest discomfort	1 (25.0)	0	1 (1.4)	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	1 (25.0)	0	7 (10.0)	0	10 (15.9)	1 (1.6)
Back pain	1 (25.0)	0	11 (15.7)	0	8 (12.7)	0
Bone pain	1 (25.0)	1 (25.0)	8 (11.4)	0	8 (12.7)	1 (1.6)
Musculoskeletal pain	1 (25.0)	0	4 (5.7)	0	4 (6.3)	0
Musculoskeletal chest pain	1 (25.0)	0	7 (10.0)	0	2 (3.2)	0
Joint swelling	1 (25.0)	0	1 (1.4)	0	0	0
Musculoskeletal discomfort	1 (25.0)	0	1 (1.4)	0	0	0
Pain in jaw	1 (25.0)	0	2 (2.9)	0	0	0
Investigations						
Aspartate aminotransferase increased	0	0	12 (17.1)	2 (2.9)	10 (15.9)	0
Alanine aminotransferase increased	0	0	11 (15.7)	2 (2.9)	7 (11.1)	1 (1.6)
C-reactive protein increased	0	0	11 (15.7)	3 (4.3)	5 (7.9)	0
Weight decreased	1 (25.0)	0	12 (17.1)	2 (2.9)	5 (7.9)	0
Blood alkaline phosphatase increased	0	0	14 (20.0)	2 (2.9)	4 (6.3)	2 (3.2)
Blood creatine phosphokinase increased	1 (25.0)	0	0	0	4 (6.3)	1 (1.6)
Fibrin D dimer increased	1 (25.0)	0	0	0	1 (1.6)	0
Neutrophil count decreased	1 (25.0)	1 (25.0)	3 (4.3)	3 (4.3)	0	0
Nervous system disorders						
Headache	1 (25.0)	0	19 (27.1)	1 (1.4)	8 (12.7)	0
Dizziness	1 (25.0)	0	13 (18.6)	0	4 (6.3)	0
Somnolence	1 (25.0)	0	4 (5.7)	0	3 (4.8)	0
Tremor	1 (25.0)	0	7 (10.0)	0	2 (3.2)	0
Skin and subcutaneous tissue disorders						
Rash	0	0	4 (5.7)	0	7 (11.1)	1 (1.6)
Respiratory, thoracic and mediastinal disorders						
Cough	3 (75.0)	0	15 (21.4)	0	10 (15.9)	0
Dyspnoea	1 (25.0)	0	6 (8.6)	1 (1.4)	4 (6.3)	2 (3.2)
Nasal congestion	1 (25.0)	0	7 (10.0)	0	3 (4.8)	0
Sinus congestion	1 (25.0)	0	1 (1.4)	0	3 (4.8)	0
Hiccups	1 (25.0)	0	1 (1.4)	0	1 (1.6)	0
Oropharyngeal pain	1 (25.0)	0	8 (11.4)	0	1 (1.6)	0
Dyspnoea exertional	2 (50.0)	0	5 (7.1)	0	0	0
Vascular disorders						
Hypotension	0	0	12 (17.1)	1 (1.4)	9 (14.3)	0
Hypertension	1 (25.0)	0	7 (10.0)	3 (4.3)	8 (12.7)	2 (3.2)
Psychiatric disorders						
Confusional state	0	0	10 (14.3)	2 (2.9)	7 (11.1)	0
Insomnia	0	0	8 (11.4)	0	3 (4.8)	0
Anxiety	0	0	11 (15.7)	0	2 (3.2)	1 (1.6)
Injury, poisoning and procedural complications						
Epicondylitis	1 (25.0)	0	0	0	0	0
Rib fracture	1 (25.0)	0	0	0	0	0
Cardiac disorders						
Tachycardia	1 (25.0)	0	14 (20.0)	0	4 (6.3)	0

SOC	Number of patients (%)					
	150×10^6 cells		300×10^6 cells		450×10^6 cells	
PT	N = 4		N = 70		N = 63	
(MedDRA/J ver.22.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders						
Periorbital oedema	1 (25.0)	0	0	0	0	0

Serious adverse events were observed in 4 of 4 patients (100%) at the target dose of 150×10^6 cells, in 46 of 70 patients (65.7%) at 300×10^6 cells, and in 44 of 63 patients (69.8%) at 450×10^6 cells. Serious adverse events observed in ≥2 patients at any target dose were febrile neutropenia and CRS in 2 patients (50%) each at the target dose of 150×10^6 cells; general physical health deterioration in 14 patients (20%), CRS in 11 patients (15.7%), pneumonia and febrile neutropenia in 5 patients (7.1%) each, sepsis in 4 patients (5.7%), C-reactive protein increased in 3 patients (4.3%), thrombocytopenia, neutropenia, pyrexia, syncope, confusional state, mental status changes, dyspnoea, and hypotension in 2 patients (2.9%) each at 300×10^6 cells; and CRS in 9 patients (14.3%), pneumonia and general physical health deterioration in 7 patients (11.1%) each, thrombocytopenia in 5 patients (7.9%), influenza, neutropenia, and basal cell carcinoma in 4 patients (6.3%) each, sepsis, pyrexia, and encephalopathy in 3 patients (4.8%) each, and hepatitis E, pneumonia pseudomonal, febrile neutropenia, asthenia, haemophagocytic lymphohistiocytosis, aphasia, lethargy, confusional state, delirium, dyspnoea, and acute kidney injury in 2 patients (3.2%) each at 450×10^6 cells. A causal relationship to Abecma could not be ruled out for CRS in 2 patients and febrile neutropenia in 1 patient at the target dose of 150×10^6 cells; CRS in 11 patients, C-reactive protein increased in 3 patients, thrombocytopenia, neutropenia, and pneumonia in 2 patients each, febrile neutropenia, confusional state, dyspnoea, and pyrexia in 1 patient each at 300×10^6 cells; and CRS in 9 patients, thrombocytopenia in 3 patients, febrile neutropenia, haemophagocytic lymphohistiocytosis, neutropenia, confusional state, delirium, aphasia, encephalopathy, and lethargy in 2 patients each, and influenza, pneumonia, dyspnoea, and asthenia in 1 patient each at 450×10^6 cells.

10. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

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

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

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

The new regenerative medical product application data (CTD 5.3.5.2.1-2) 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.

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

On the basis of the data submitted, PMDA has concluded that Abecma has a certain level of efficacy in the treatment of "Relapsed or refractory multiple myeloma (Abecma should be used only in patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy)," and that Abecma has acceptable safety in view of its benefits. Accordingly, it is of significance to make Abecma available in clinical practice because it offers a new treatment option for patients with MM.

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

Review Report (2)

November 15, 2021

Product Submitted for Approval

Brand Name	Abecma Intravenous Infusion
Non-proprietary Name	Idecabtagene Vicleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 31, 2021

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

On the basis of review in Section "7.R.1 Efficacy" of the Review Report (1), the overall response rate, the primary efficacy endpoint of Study MM-001 conducted in patients with relapsed or refractory MM, was greater than the predefined efficacy threshold. PMDA, therefore, concluded that a certain level of efficacy of Abecma has been demonstrated in patients with relapsed or refractory MM.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "7.R.2 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention in Abecma treatment are CRS, haemophagocytic lymphohistiocytosis, neurologic toxicity, infection, cytopenia, hypersensitivity, hypogammaglobulinaemia, and TLS. Caution should be exercised against these adverse events in the use of Abecma.

In addition, PMDA concluded that Abecma is tolerable, given appropriate measures i.e., monitoring and management of adverse events taken by a physician with sufficient knowledge and experience in the treatment of MM at a medical institution well-equipped for dealing with these adverse events.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indication or performance

As a result of the review in Section "7.R.3 Clinical positioning and indication or performance" of the Review Report (1), PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be described as per the relevant sections of the Review Report (1). However, after the finalization of the Review Report (1), it was considered appropriate to clearly state in "Indication or Performance" that patients with a prior BCMA-targeted CAR-expressing T cell infusion therapy are excluded for the treatment with Abecma, in relation to the conclusion that retreatment with Abecma is not recommended [see Section 7.R.4.5 of the Review Report (1)]. Accordingly, PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be described as follows:

Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

Precautions Concerning Indication or Performance

Patients considered appropriate to receive Abecma must be selected by physicians who have fully understood the efficacy and safety of Abecma after being thoroughly familiar with prior treatment, etc. of patients enrolled in the clinical studies described in the "Clinical Studies" section.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA requested the applicant to modify the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.4 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections should be described as per the relevant sections of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

On the basis of the discussion at the Expert Discussion on the aggravation of graft versus host disease in "1.5 Post-marketing surveillance plan (draft)," PMDA concluded that the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections should be modified as follows:

Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280 × 10^6-540 × 10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

Precautions Concerning Dosage and Administration or Method of Use

Refer to the manufacturer's manual for details on the steps from the collection of cells from the patient through the administration of Abecma.

If any of the following conditions is observed in the patient, postpone lymphodepleting chemotherapy or Abecma infusion until recovery.

- Persisting serious adverse events (lung disorder, cardiac disorder, hypotension, etc.) caused by the preceding chemotherapy
- Active infection and inflammatory disease

Pretreatment

In order to facilitate the engraftment of transplanted cells, Abecma infusion should be preceded by administration of chemotherapeutic agents with a cytocidal effect such as DNA synthesis inhibitory activity or immunosuppressive activity associated with a decrease in lymphocyte count. See the "Clinical Studies" section for the details of the pretreatment given in the clinical studies.

Administration of Abecma

1. Confirm the scheduled infusion timing in advance, and adjust the time to start thawing Abecma so that infusion can be started as soon as the patient is ready.
2. In order to minimize the risk of infusion reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker approximately 30 to 60 minutes before the infusion of Abecma. Do not use corticosteroids unless a life-threatening emergency arises. Be prepared for emergency treatment of a severe event such as anaphylaxis following Abecma infusion.
3. Ensure that tocilizumab (genetical recombination) is available for prompt use in case of emergency with cytokine release syndrome.
4. Before thawing Abecma, confirm that the patient identity matches the information on the metal cassette and the infusion bag. Then remove the infusion bag from the metal cassette.
5. Do not use Abecma if any damage or leaks are noticed on the infusion bag.
6. Abecma is supplied as one or more infusion bags containing CAR-expressing T cell suspension. If 2 or more bags are used, do not start thawing of the second and subsequent infusion bags until administration of Abecma in the first infusion bag is completed.
7. Thaw Abecma in the infusion bag completely in a thermostat bath or a dry thawing device, etc., at approximately 37°C. If clumps of cellular material are visible, swirl the infusion bag slowly. Do not refreeze the thawed Abecma. After thawing is completed, remove the infusion bag promptly from the bath. Do not wash, spin down, or resuspend cells in a new culture medium before infusion.
8. Do not irradiate Abecma. Do not use a leukodepleting filter for Abecma infusion.
9. Prior to infusion, confirm that the patient's identity matches the patient identifiers on the Abecma infusion bag.
10. Prime the tubing with physiological saline before Abecma infusion. After the entire content of the infusion bag is infused, rinse the infusion bag with physiological saline by backpriming to ensure delivery of as many cells as possible.
11. Complete infusion within 1 hour after the start of thawing Abecma.
12. If more than one infusion bags have been received, administer all bags as directed on the Release for Infusion Certificate. Follow the same procedure as in the first infusion bag above for the second and subsequent infusion bags.
13. Abecma contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. The residual Abecma suspension should be disposed of as infectious waste in accordance with the universal precautions and local biosafety guidelines.

PMDA requested the applicant to modify the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHOD OF USE sections as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.5 Post-marketing surveillance plan (draft)

At the time of application, the applicant proposed a plan of post-marketing surveillance covering all patients treated with Abecma to evaluate the safety, etc. of Abecma in clinical use. The planned sample size was 200. The planned observation period was up to 8 years.

As a result of the review in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA concluded that "haemophagocytic lymphohistiocytosis" and "hypersensitivity" should be added to the safety specifications of the post-marketing surveillance plan.

After the finalization of the Review Report (1), an investigation on "aggravation of graft versus host disease," a risk included in the safety specifications, revealed that there was no use experience of Abecma in patients with a history of allogeneic hematopoietic stem cell transplantation in Studies CRB-401 and MM-001 and therefore that Abecma administration to this patient group is not recommended. Accordingly, "aggravation of graft versus host disease" should be deleted from the safety specifications of Abecma.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

PMDA requested the applicant to modify the post-marketing surveillance plan based on the results of the Expert Discussion. In response, the applicant submitted an outline of the post-marketing surveillance plan (draft) shown in Table 57, and PMDA accepted the draft plan.

Table 57. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety, etc. of Abecma in clinical use
Survey method	All-case surveillance The applicant will obtain data of the target population from the data compiled in the registry database (FormsNet) owned by the Center for International Blood and Marrow Transplant Research (CIBMTR) via the Japanese Data Center for Hematopoietic Cell Transplantation.
Population	Patients with relapsed or refractory MM
Observation period	Up to 8 years
Planned sample size	200 patients
Main survey items	Safety specifications CRS, nervous system events, cytopenia, hypogammaglobulinaemia, infection, haemophagocytic lymphohistiocytosis, hypersensitivity, secondary malignancies (including oncogenesis due to insertional mutagenesis caused by lentiviral vector), TLS, impact on pregnancy and lactation, long-term safety, and safety in elderly patients

1.6 Others

1.6.1 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (PFSB/ELD Notification No. 1105-1 and PFSB/ELD/OMDE Notification No. 1105-2, both dated November 5, 2014), PMDA has concluded that Abecma need not be designated as a specified regenerative medical product for the following reasons:

- Except for FBS that is used in the preparation of MCB, which is used for the manufacture of the viral vector, all other human-and animal-derived components used for the manufacture of Abecma meet the Standards for Biological Ingredients, with a resultant extremely low risk of causing infection.
- As for FBS used in the preparation of MCB, which is used for the manufacture of the viral vector, it is extremely unlikely to be contaminated by viruses of bovine origin and thus has an acceptable, although not completely excluded, risk of contamination, for the following reasons: (a) The MCB prepared using said FBS has been confirmed to be free from viruses of bovine origin by tests for bovine viruses as shown in Table 1 in 2.1.2 of the Review Report (1); and (b) FBS has been confirmed to meet the criteria for ensuring a certain level of safety against BSE.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance as well as dosage and administration or method of use refined as below, with the following approval conditions, based on the premise that the provision of cautionary advice via the package insert and the dissemination of information on proper use of the product are appropriately implemented in the post-marketing setting. Because the product is classified as an orphan regenerative medical product, the re-examination period should be 10 years. The product need not be designated as a designated regenerative medical product.

Indication or Performance

Relapsed or refractory multiple myeloma. Abecma should be used only in patients meeting all of the following criteria:

- Patients with no history of BCMA-targeted chimeric antigen receptor-expressing T cell infusion therapy
- Patients who have received at least 3 prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and showed disease progression or relapse after the last prior therapy

Dosage and Administration or Method of Use

Process from leukapheresis at a medical institution to transportation to a manufacturing facility

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a refrigerated container maintained at 2°C to 8°C and transported to a manufacturing facility of Abecma.

Process from receipt at the medical institution to administration of Abecma

3. Receipt and storage of Abecma
   Abecma is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before Abecma administration
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 5 days prior to Abecma administration.
   Administer cyclophosphamide (anhydrate) 300 mg/m^2 as an intravenous infusion once daily for 3 days and fludarabine phosphate 30 mg/m^2 as an intravenous infusion once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Administration of Abecma
   Abecma is thawed immediately before infusion. The usual adult dosage is the target dose of 450 × 10^6 cells (range, 280 × 10^6-540 × 10^6 cells) of CAR-expressing T cells, irrespective of body weight, administered intravenously as a single dose at an infusion rate not exceeding 10 mL/min. Retreatment with Abecma is not allowed.

Approval Conditions

1. The applicant is required to ensure that the product is used by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation at a medical institution that can properly respond to emergencies in an environment that ensures appropriate actions (e.g., management of cytokine release syndrome) are taken.
2. Since only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been collected, in order to understand the characteristics of patients using the product, and promptly collect safety and efficacy data so that necessary measures are taken to ensure the proper use of the product.

Appendix

List of Abbreviations

Abecma	Abecma Intravenous Infusion
[redacted]	[redacted]
ALL	acute lymphoblastic leukemia
Anti-BCMA CAR	Anti-BCMA chimeric antigen receptor
Anti-CD19 CAR	Anti-CD19 chimeric antigen receptor
Application	Application for marketing approval
ATCC	American Type Culture Collection
$AUC_{0\text{-}28days}$	area under the curve of the transgene level from time of dose to 28 days postinfusion
$AUC_{0\text{-}3M}$	area under the curve of the transgene level from time of dose to 3 months postinfusion
$AUC_{0\text{-}6M}$	area under the curve of the transgene level from time of dose to 6 months postinfusion
$AUC_{0\text{-}9M}$	area under the curve of the transgene level from time of dose to 9 months postinfusion
BAV	bovine adenovirus
BCMA	B cell maturation antigen
BL	Burkitt's lymphoma
bluebird bio	bluebird bio, Inc.
BPV	bovine parvovirus
BRSV	bovine respiratory syncytial virus
[redacted]	[redacted]
BSE	bovine spongiform encephalopathy
BTV	bluetongue virus
[redacted] cells	[redacted] cells
BVDV	bovine viral diarrhea virus
CAR	chimeric antigen receptor
CD	cluster of differentiation
Celgene	Celgene Corporation
CLL	chronic lymphocytic leukemia
C_{max}	maximum transgene level
CMV	cytomegalovirus
Component cells	Cells constituting Abecma
CPE	cytopathic effect
CQA	critical quality attribute
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CV	coefficient of variation
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
[redacted] cells	[redacted]
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EPC	end of production cell
EVA	ethylene vinyl acetate
FBS	fetal bovine serum
FLC	free light chain

Fludarabine	Fludarabine Phosphate
GALV	gibbon ape leukemia virus
GC	guanine-cytosine
gDNA	genomic DNA
[redacted]	[redacted]
HA	hemagglutination
HBV	hepatitis B virus
HCV	hepatitis C virus
HEK293 cells	Human Embryonic Kidney 293 cells
HEK293T cells	Human Embryonic Kidney 293T cells
[redacted] cells	[redacted] cells
[redacted]	[redacted]
HHV	human herpes virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HSA	human serum albumin
HTLV	human T-cell leukemia virus
ICU	intensive care unit
IFN-γ	interferon-gamma
IHC	immunohistochemistry
IL	interleukin
IMWG	International Myeloma Working Group
IMWG Criteria	Criteria established by IMWG
IRC	Independent Response Committee
LD chemotherapy	lymphodepleting chemotherapy
LTR	long terminal repeat
MCB	master cell bank
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
ML	myelogenous leukemia
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
[redacted] cells	[redacted] cells
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NE	not evaluable
NHL	non-Hodgkin lymphoma
NK cells	natural killer cells
NSG	NOD-Cg-Prkdc^{scid} IL2rg^{tm1Wjl}/SzJ
OIE	International Epizootic Office
OS	overall survival
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PHEV	porcine hemagglutinating encephalitis virus
PK15 cells	porcine kidney 15
PMDA	Pharmaceuticals and Medical Devices Agency
[redacted]	[redacted]
PPV	porcine parvovirus

PR	partial response
PS	performance status
PT	preferred term
PVB19	parvovirus B19
QbD	quality by design
qPCR	quantitative polymerase chain reaction
[redacted]	[redacted]
RABV	rabies virus
RCL	replication competent lentivirus
RCR	replication competent retrovirus
Reo	reo virus
RP2D	recommended Phase 2 dose
[redacted]	[redacted]
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
sBCMA	soluble BCMA
scFv	single-chain variable fragment
sCR	stringent complete response
SD	stable disease
[redacted] cells	[redacted]
SIN	self-inactivating
SMQ	standardised MedDRA queries
SOC	system organ class
Study MM-001	Study BB2121-MM-001
Study MM-002	Study BB2121-MM-002
[redacted]	[redacted]
TGEV	transmissible gastroenteritis virus
T_{last}	time of last measurable transgene level
TLS	tumor lysis syndrome
T_{max}	time of maximum observed transgene level
[redacted]	[redacted]
Tocilizumab	Tocilizumab (Genetical Recombination)
[redacted]	[redacted]
Vero cells	African green monkey kidney epithelial cells
VGPR	very good partial response
VSV-G	glycoprotein of the vesicular stomatitis virus
WCB	working cell bank