August 3, 2022
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	Ciltacabtagene autoleucel
Brand Name	Carvykti Suspension for Intravenous Infusion
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on August 3, 2022, 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. Because only a limited number of Japanese patients participated in the clinical study of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a specified number of patients have been collected, in order to understand the characteristics of patients using the product and to collect safety and efficacy data as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Review Report

July 14, 2022
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	Carvykti Suspension for Intravenous Infusion
Classification	Human cellular/tissue-based products, 1. Human somatic cell processed product
Non-proprietary Name	Ciltacabtagene autoleucel
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a genetically modified T cell immunotherapy product consisting of autologous human T cells transduced *ex vivo* using a lentiviral vector encoding an anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR).

Application Classification (1-1) New regenerative medical product

Items Warranting Special Mention

Orphan regenerative medical product (Orphan Regenerative Medicinal Product Designation No. 18 of 2020 [*R2 sai*]; PSEHB/MDED Notification No. 0623-3 dated June 23, 2020, issued by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

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

Indication or Performance

Relapsed or refractory multiple myeloma. Carvykti must be used only in patients meeting both of the following criteria.

- Patients who are naïve to BCMA-targeted chimeric antigen receptor T-cell infusion therapy
- Patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and who have failed to respond to or have relapsed after the last therapy

Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to 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 transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti
   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at ≤−120°C) until immediately before use.
4. Pretreatment before administration of Carvykti
   Check the patient's condition by blood tests etc. Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion.
   Administer cyclophosphamide 300 mg/m^2(on the anhydrous basis) intravenously once daily for 3 days and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
5. Administration of Carvykti
   Carvykti is thawed immediately before administration. The usual target dose in adults is 0.75×10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion at a rate of ≤7 mL/min. The acceptable dose range is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0×10^8 CAR-positive viable T cells). Do not re-administer Carvykti.

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. Because only a limited number of Japanese patients participated in the clinical study of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a specified number of patients have been collected, in order to understand the characteristics of patients using the product and to collect safety and efficacy data as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

May 27, 2022

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

Product Submitted for Approval

Brand Name	Carvykti Suspension for Intravenous Infusion
Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Ciltacabtagene autoleucel
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 2021

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a genetically modified T cell immunotherapy product consisting of autologous human T cells transduced *ex vivo* using a lentiviral vector encoding an anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR).

Proposed Indication or Performance

Relapsed or refractory multiple myeloma. Carvykti should be used only in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody.

Proposed Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   White blood cells including sufficient T-lymphocytes are collected.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti
   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at ≤−120°C) until immediately before use.
4. Pretreatment before administration of Carvykti
   Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion. Administer

cyclophosphamide 300 mg/m^2 (on the anhydrous basis) and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

If resolution of Grade ≥3[Note)] toxicities due to the lymphodepleting chemotherapy to Grade 1[Note)] or lower takes ≥14 days, thereby resulting in delays in Carvykti dosing, the lymphodepleting chemotherapy should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting chemotherapy.

Note) Toxicities are graded according to the NCI-CTCAE v5.0.

5. Administration of Carvykti

Carvykti is thawed immediately before administration. The usual recommended dose range in adults is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion (with a maximum dose of 1.0×10^8 CAR-positive viable T cells).

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

Carvykti (ciltacabtagene autoleucel), a regenerative medical product, is comprised of cultured autologous peripheral T cells that have been transduced with a recombinant lentiviral vector encoding a chimeric antigen receptor (CAR) that specifically recognizes B-cell maturation antigen (BCMA). Carvykti is infused intravenously into the patient to obtain a therapeutic effect based on the pharmacological action, in the same manner as drugs.

The CAR of Carvykti is comprised of 2 llama-derived variable fragments of heavy chain antibodies (VHH1 and VHH2) specific for recognizing BCMA antigen, a human CD8α hinge and transmembrane domain, and human 4-1BB and CD3ζ cytoplasmic signalling domains. The effector functions of transduced T-cells are induced through recognition of BCMA-expressing cells, e.g., T-cell activation, expansion, and cytotoxicity. These actions of Carvykti are expected to eliminate BCMA-positive tumor cells.

Carvykti was designated as an orphan regenerative medical product with the intended indication or performance of “relapsed or refractory multiple myeloma” on June 23, 2020 (Orphan Regenerative Medicinal Product Designation No. 18 of 2020 [*R2 sai*]).

1.2 Development history etc.

Multiple myeloma (MM) is a malignant disorder of plasma cells differentiated from B lymphocytes, characterized by uncontrolled and progressive proliferation of plasma cells and increased levels of monoclonal immunoglobulins (M-protein) produced by myeloma cells in the serum or urine (Clinical Practice Guidelines for Tumors of Hematopoietic and Lymphoid Tissues 2018, Revised Edition. Kanehara & Co., Ltd.; 2020: p320). The disease presents with a variety of clinical symptoms and leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant bone lesions (with bone pain, pathologic fractures, and hypercalcemia), renal insufficiency, anemia, hyperviscosity, and secondary amyloidosis (*Cancer Cell*. 2013; 24: 275-7).

The treatment paradigm for MM underwent significant evolution in recent years with the development of new therapeutic agents such as immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies (*Pharmacother*. 2017; 37: 129-43). On the other hand, despite these advances in available therapeutic options, all patients eventually relapse and become refractory to existing treatments. With each successive relapse, symptoms return, quality of life (QOL) worsens, and the chance and duration of response (DOR) typically decrease. The median overall survival (OS) in patients with MM who have received at least 3 prior lines of therapy and are refractory to both an immunomodulatory drug and a proteasome inhibitor is 13 months (*Leukemia*. 2017; 31: 2443-8). The reported overall response rate (ORR) for approved therapies in the population of heavily pre-treated patients with relapsed or refractory MM, is approximately 30% or less (*Lancet Oncol.* 2013; 14: 1055-66, *Leukemia*. 2017; 31: 107-14, etc.). Based on the above, there is an unmet medical need for new treatment options directed at alternative mechanisms of action that can achieve deeper and more

durable responses and improve QOL.

Outside Japan, Legend initiated a phase I study of Carvykti in patients with relapsed or refractory MM (the Legend-2 study) in March 2016. Then, Janssen Biotech undertook a global phase Ib/II study in patients with relapsed or refractory MM (Study MMY2001) in July 2018.

In the US, Carvykti was approved for the following indication or performance in February 2022, based on the results from the pivotal study MMY2001: "CARVYKTI 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 a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody."

In the EU, Carvykti was approved for the following indication or performance in May 2022, based on the results from the pivotal study MMY2001: "CARVYKTI 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, Janssen Pharmaceutical K.K. started patient enrollment in Study MMY2001 in December 2019.

A marketing application for Carvykti has been filed based on the results from the pivotal study MMY2001.

2. Quality and Outline of the Review Conducted by PMDA

Carvykti is an autologous cell suspension of transduced CAR T cells. Carvykti is prepared from the patient's peripheral blood mononuclear cells (PBMCs), which are obtained via a leukapheresis procedure. T cells in the PBMCs are activated and transduced with a viral vector encoding an anti-human BCMA CAR. The transduced anti-BCMA CAR T cells are expanded in cell culture and formulated into a suspension.

2.1 Viral vector

The viral vector used to transduce autologous T cells is a HIV-1-derived replication-incompetent lentiviral vector with a self-inactivating (SIN) long terminal repeat (LTR). The anti-BCMA CAR to be transduced via the viral vector is comprised of a human BCMA binding domain,[1)] a human CD8α hinge and transmembrane domain, and human 4-1BB and CD3ζ cytoplasmic signalling domains.

The viral vector genome contains HIV-1-derived 5'LTR, packaging signal (Ψ), [redacted], [redacted], hEF1α promoter,

[1)] Multiple VHHs that specifically bind to human BCMA protein were isolated from a phage display library constructed from llama immunized with recombinant human BCMA protein and sequenced. Anti-human BCMA CAR expression constructs were generated using codon-optimized VHHs. Multiple VHHs with high activity were selected based on [redacted] and [redacted] to [redacted]. Various dual epitope-binding CAR expression constructs were generated by inserting a linker between 2 different VHHs. The optimal combination of VHHs was selected based on activity and used as the human BCMA-binding domain of Carvykti.

anti-BCMA CAR transgene, [redacted], and [redacted]3'LTR. A large portion of the HIV-1 genome is deleted from the viral vector genome. The genes encoding Gag/Pol, Rev, and VSV-G, which are required for viral vector production, are separated into different plasmid vectors. The viral vector has been designed to avoid the generation of a replication-competent virus by homologous recombination.

2.1.1 Plasmids

A transfer plasmid and 3 helper plasmids are used for viral vector manufacturing. The transfer plasmid contains an expression construct, which expresses anti-BCMA CAR under the control of hEF1α promoter. The helper plasmids contain expression constructs, which express Gag/Pol or VSV-G under the control of [redacted] or Rev under the control of [redacted]. The controls of the plasmids consist of [redacted], endotoxin, [redacted], and sterility.

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

Human embryonic kidney 293F (HEK293F) cells ([redacted]; [redacted]) obtained from [redacted] were used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and end of production cells (EPC) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1) and Q5D guidelines. Tests for adventitious agents conducted are shown in Table 1. No viral or non-viral adventitious agents were detected in any of the tests conducted.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

Table 1. Tests for adventitious agents

In vitro virus tests (MRC-5 cells, Vero cells, and 293 cells)
In vivo virus tests (suckling and adult mice, guinea pigs, and embryonated eggs)
In vitro tests for bovine viruses (BTV, BAV, BPV, BRSV, BVDV, IBR, PI3, RABV, and REO3 [BT cells and Vero cells], BHV [qPCR])
In vitro tests for porcine viruses (BVDV, PI3, PAV, HEV, PPV, RABV, REO3, TGEV [PT-1 cells and HCT-8 cells], PCV [qPCR])
In vitro tests for human viruses (EBV, HAV, HBV, HCV, HSV-1, HSV-2, HHV-5/hCMV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1, HTLV-2, PVB19, SV40, HuPyV, AAV-5, HPV, EV, RUBV, VZV, and WNV)
Transmission electron microscopy
Reverse transcriptase activity assay
Infectivity assay (Feline S^+ L^-)
Mycobacteria assay
Sterility testing
Mycoplasma assay

2.1.3 Viral vector manufacturing process

The viral vector manufacturing process consists of preculture and expansion, [redacted], clarification of the harvest, [redacted], [redacted], [redacted], filling and storage, and testing.

[redacted], [redacted], and [redacted] have been defined as critical steps.

Process validation of the commercial-scale viral vector manufacturing process has been performed.

2.1.4 Adventitious agents safety evaluation of viral vector

Table 2 shows the raw materials of biological origin other than HEK293F cells used in the viral vector manufacturing process, all of which have been confirmed to conform to the Standards for Biological Ingredients.

Table 2. Raw materials of biological origin other than HEK293F cells

Raw material	Animal species	Specific part used	Process step
Human transferrin	Human	Blood	[redacted]
Casein acid hydrolysate	Bovine	Milk	[redacted]
HSA	Human	Blood	[redacted]

For [redacted] after the end of production culture for the viral vector, tests for adventitious agents are performed as specification tests for the viral vector [see Section 2.1.7].

2.1.5 Viral vector manufacturing process development

Major changes made to the viral vector manufacturing process during development are shown below. Table 3 shows the manufacturing processes for the viral vectors used for the manufacture of the finished products used in non-clinical and clinical studies.

- Process A → Process B: changes to [redacted], [redacted], [redacted], and [redacted], and addition of [redacted] and [redacted]
- Process B → Process C: change of [redacted]
- Process C → Process D (the proposed commercial process): changes to [redacted], [redacted], [redacted], [redacted], and [redacted]

Comparability studies on quality attributes were performed for these process changes. Although [redacted] with Process D compared to Process C, [redacted]. The comparability of quality attributes between pre-change and post-change viral vector products has been demonstrated for this process change[2)] [see Section 2.2.4]. Thus, the applicant explained that there is no problem. The comparability of quality attributes between pre-change and post-change viral vectors has also been demonstrated for other process changes.

2) Change from Process V to Process VI (Proposed commercial process)

Table 3. Manufacturing processes for viral vectors used for manufacture of finished products used in non-clinical and clinical studies

Process	Non-clinical or clinical studies
Process A	[redacted] study, [redacted] study
Process B	[redacted] study, [redacted] study, [redacted] study
Process C	[redacted] study, [redacted] study, [redacted] study, [redacted] study
Process D (Proposed commercial process)	[redacted] study, [redacted] study, [redacted] study

2.1.6 Characterization of viral vector

2.1.6.1 Structure and properties

Table 4 shows characterization tests performed.

Table 4. Characterization attributes of viral vector

Characterization of viral vector	viral vector genome sequence, [redacted], osmolality, proviral sequence, product-related particles (host cell proteins, media proteins, viral proteins), impurities (RCL, host cell DNA [Impurity A, Impurity B, [redacted] and [redacted] of Impurity C], plasmid DNA, host cell proteins, Impurity D)

2.1.6.2 Product-related impurities/process-related impurities

Replication-competent lentivirus (RCL) and product-related particles have been defined as product-related impurities. Host cell DNA (Impurity A, Impurity B, [redacted] and [redacted] of Impurity C), plasmid DNA, host cell proteins, and Impurity D have been defined as process-related impurities. The process-related impurities have been demonstrated to be adequately removed in the manufacturing process. RCL, host cell DNA (Impurity A, Impurity B, [redacted] and [redacted] of Impurity C), plasmid DNA, host cell proteins, and Impurity D are controlled by the viral vector specification. No RCLs have been detected in the batches manufactured to date.

2.1.7 Control of viral vector

The proposed viral vector specifications consist of appearance, identity ([redacted]), pH, purity (host cell DNA [Impurity A, Impurity B, [redacted] and [redacted] of Impurity C], host cell proteins, Impurity D, plasmid DNA), endotoxin, sterility, virus testing (*in vitro* virus tests for [redacted] [Vero cells, MRC-5 cells, HeLa cells]), mycoplasma (test for [redacted]), RCL ([redacted] for [redacted] and [redacted]), potency (infectious titer, anti-BCMA CAR expression by transduction of [redacted], IFN-γ secretion by anti-BCMA CAR-positive T cells), assay (quantity of [redacted]), and [redacted].

2.1.8 Stability of viral vector

Primary stability studies on viral vector are outlined in Table 5.

Table 5. Overview of primary stability studies on viral vector

Study	Process	Number of batches	Storage conditions	Testing period	Storage package
Long-term	Proposed commercial process	4	[redacted] ± [redacted]°C	[redacted] months	[redacted] vial with [redacted] rubber stopper
Accelerated	Proposed commercial process	4	[redacted] ± [redacted]°C	[redacted]	

The long-term testing ([redacted] ± [redacted]°C) and the accelerated testing ([redacted] ± [redacted]°C) showed no significant changes in quality attributes throughout the testing period.

Based on the above findings, a shelf-life of [redacted] months has been proposed for the viral vector when stored in [redacted] vial with [redacted] rubber stopper at [redacted] ± [redacted]°C.

2.2 Finished product

2.2.1 Description and composition of finished product and formulation development

The finished product containing anti-BCMA CAR-positive T cells is filled in either of two ethylene vinyl acetate (EVA) cryostorage bags, depending on the final volume.[3)] The viable cell count per bag is adjusted to an appropriate target range based on patient weight as indicated in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section of the package insert. The finished product contains CryoStor CS5 as an excipient.

2.2.2 Manufacturing process

The finished product manufacturing process consists of [redacted], thawing of the frozen apheresis material and T cell enrichment, T cell activation, T cell transduction and expansion, T cell harvest and washing, [redacted], filling and cryopreservation, and testing.

[redacted], [redacted], and [redacted] have been defined as critical steps.

Process validation of the commercial-scale finished product manufacturing process has been performed.

2.2.3 Adventitious agents safety evaluation

2.2.3.1 Patient-derived peripheral blood mononuclear cells

The raw material of the finished product, i.e., patient-derived PBMCs meet the requirements for the method of collection, the record, etc., specified in the standards for raw materials of human cellular/tissue-based products of the Standards for Biological Ingredients (MHLW Public Notice No. 210 of 2003). Prior to apheresis, a patient history is taken at the medical institution, and the patient has tests for infections (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]) as needed.

2.2.3.2 Raw materials of biological origin other than patient-derived PBMCs

Table 6 shows the raw materials of biological origin other than patient-derived PBMCs used in the manufacturing process, all of which have been confirmed to conform to the Standards for Biological Ingredients.

[3)] Two types of bags with different volumes (50-mL and 250-mL bags) are used, and 30 and 70 mL of cell suspension are filled into these bags, respectively.

Table 6. Raw materials of biological origin other than patient-derived PBMCs used in manufacturing process

Raw material	Animal species	Specific part used	Process step
HSA (1)	Human	Blood	[redacted]
Anti-[redacted] antibody	Murine	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Murine	Hybridoma cells	[redacted]
HSA (2)*	Human	Blood	[redacted]

* [redacted]

2.2.4 Manufacturing process development

Table 7 shows major changes made to the finished product manufacturing process during development. Table 8 shows the manufacturing processes for the finished products used in non-clinical or clinical studies. For these manufacturing processes, [redacted] at different manufacturing sites according to [redacted] or [redacted]. These steps take place [redacted].

For these process changes, the comparability of quality attributes between pre-change and post-change finished products has been demonstrated.

Table 7. Changes to finished product manufacturing process

Process	Changes etc.
Process I → Process II	Change of [redacted], change for [redacted], change of [redacted], change of [redacted], change of [redacted]
Process II → Process III	Change of [redacted], change of [redacted], change of [redacted]
Process III → Process IV	Change of [redacted], change of [redacted], change of [redacted]
Process IV → Process V	Change of [redacted]
Process V→Process VI (Proposed commercial process)	Change of [redacted]

Table 8. Manufacturing processes for finished products used in non-clinical or clinical studies

Process	Non-clinical or clinical studies
Process I	Non-clinical study, Legend-2 study
Process II	Non-clinical study, Study MMY2001
Process III	Non-clinical study, Study MMY2001
Process IV	Non-clinical study, Study MMY2001, Study MMY2003
Process V	Non-clinical study, Study MMY2001, Study MMY2003, Study MMY3002
Process VI (Proposed commercial process)	Study MMY2003, Study MMY3002

2.2.5 Characterization

2.2.5.1 Structure and properties

Table 9 shows characterization tests performed.

Table 9. Characterization attributes of anti-BCMA CAR-T cells

Structure and cytological properties	T-cell subset analysis ([redacted]), viral vector integration site analysis [see Section 5.2.1]
Biological properties	Release of cytokines ([redacted]) in response to BCMA-specific stimulation, secretion of cytotoxic factors ([redacted]), BCMA-specific [redacted]
Purity	Unintended cells ([redacted]), residual viral vector and viral vector-related impurities (Impurity E, host cell DNA, plasmid DNA, host cell proteins, Impurity D), RCL, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, Impurity L, Impurity M

2.2.5.2 Process-related impurities

Residual viral vector and viral vector-related impurities (Impurity E, host cell DNA, plasmid DNA, host cell proteins, Impurity D), RCL, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, Impurity L, and Impurity M were considered process-related impurities.

The process-related impurities excluding residual viral vector were considered to be of little safety concern in humans at estimated exposure levels per dose calculated from the estimated residual levels in the finished product. Thus, there are no controls of process-related impurities.

The capability of the proposed commercial process to remove residual viral vector was evaluated, and its residual level in the final product has been demonstrated to be below the limit of quantification ([redacted]; [redacted] copies/reaction).

RCL is controlled by the finished product specification.

2.2.6 Control of finished product

The proposed specifications for the finished product consist of appearance, identity ([redacted]), purity (cell viability, [redacted], % NK cells, [redacted]), endotoxin, sterility, mycoplasma, RCL, [redacted], potency (% CAR-positive T cells, IFN-γ secretion), dose (the number of anti-BCMA CAR-positive T cells), and quantity (viable cell concentration).

2.2.7 Stability of finished product

The primary stability studies on the finished product are outlined in Table 10. [redacted] vary from batch to batch.

Table 10. Overview of primary stability studies on finished product

Study	Number of batches	Process	Derived from:	Storage conditions	Testing period	Storage package	Fill volume /Bag size
Long-term	1	Proposed commercial process[*1]	[redacted]	≤−120℃	9 months	EVA cryostorage bag	[redacted] mL
	5	Proposed commercial process	[redacted]		9 months		
	3		[redacted]				
	1[*2]		[redacted]		[redacted] months[*3]		
	2[*2]				[redacted] months[*3]		
	3[*4]	Proposed commercial process[*5]			[redacted] months[*6]		[redacted] mL
Stress	2	Proposed commercial process	[redacted]	[redacted]			[redacted] mL
In-use stability	6			RT	[redacted]		
	2						[redacted] mL
	3		[redacted]				[redacted] mL

*1 Manufactured at [redacted].
*2 The batches [redacted].
*3 The stability studies are ongoing up to 9 months.
*4 For each batch, [redacted].
*5 [redacted]
*6 The stability study is ongoing up to 9 months. [redacted] has been obtained.

The long-term testing and the stress testing showed no significant changes in quality attributes throughout the testing period. According to the applicant's explanation, [redacted] is ongoing [redacted], and [redacted] will be submitted in the present application.

In the in-use stability study, while there were no significant changes in quality attributes at 2.5 hours post-thaw, a decreasing trend in [redacted] was observed at [redacted] post-thaw.

The applicant's explanation:
A shelf-life of 9 months has been proposed for the finished product when stored in an EVA cryostorage bag at ≤−120℃. The infusion should be completed within 2.5 hours of thawing at room temperature.

2.3 Quality control strategy

A quality control strategy was established based on the following:

- Identification of critical quality attributes (CQAs):

  The following CQAs for process-related impurities and finished product attributes were identified based on the information obtained during the development of Carvykti, the relevant knowledge, and other findings:

  ➢ CQAs of viral vector

  [redacted], sterility, endotoxin, mycoplasma, adventitious viruses, [redacted], RCL, [redacted]

  ➢ CQAs of finished product

  [redacted], sterility, endotoxin, mycoplasma, RCL, [redacted], adventitious viruses, [redacted]

- Process characterization:

  Process parameters were classified by risk assessment based on their impact on CQAs, and each process step was characterized.

- Development of method of control:

  In light of process knowledge including the above process characterization, Carvykti quality control strategy was established through the combination of the control of process parameters, in-process controls, and the specifications. As a result, the quality attributes of Carvykti were demonstrated to be adequately controlled [for the control of process-related impurities, see Section 2.2.5.2].

2.R Outline of the Review Conducted by PMDA

From the submitted data, PMDA concluded that the quality of the viral vector is adequately controlled. As to the finished product, [redacted] has not been submitted [see Section 2.2.7]. Thus, PMDA's final conclusion concerning the quality of the finished product will be presented in the Review Report (2).

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

The applicant submitted the results from the following *in vitro* and *in vivo* studies as indication or performance data. Carvykti manufactured by Process I, II, or III was used in the studies.

3.1 *In vitro* studies

3.1.1 Binding characterization of human BCMA-binding domain of Carvykti to BCMA (CTD 4.2.1.1.4[4] and 4.2.1.1.5)

The binding affinity of LAB003-His[5] to human, mouse, or rhesus monkey BCMA expressed on HEK293T cells was assessed by flow cytometry. Specific binding of LAB003-His to human BCMA was observed, but LAB003-His did not bind to mouse or rhesus monkey BCMA. The K_d value of LAB003-His for human BCMA expressed on HEK293T cells was 78.9 pmol/L (mean, n = 2). The binding affinity of LAB003-His to human, mouse, or cynomolgus monkey BCMA recombinant protein was assessed by surface plasmon resonance (SPR). LAB003-His showed a binding signal to human BCMA at 0.19 nmol/L, but not to mouse or cynomolgus monkey BCMA even at 400 nmol/L.

3.1.2 BCMA-dependent cytotoxicity induced by Carvykti (CTD 4.2.1.1.16)

Carvykti generated from a healthy donor (HD), Carvykti generated from a MM patient, or untransduced T cells generated from a healthy donor as a negative control were co-cultured with the target cells (RPMI8226.Luc cells[6] or A549.Luc cells[7]) at the effector to target cell ratios (E/T ratios) of 10:1, 5:1, 2:1, 1:1, 1:2, or 1:5, and cytotoxicity was assessed by measuring the luciferase activity of viable cells. Carvykti was not cytotoxic to A549.Luc cells with no BCMA expression, but showed an E/T ratio-dependent cytotoxicity against BCMA-expressing RPMI8226.Luc cells. On the other hand, untransduced T cells were little cytotoxic to these cells (Figure 1).

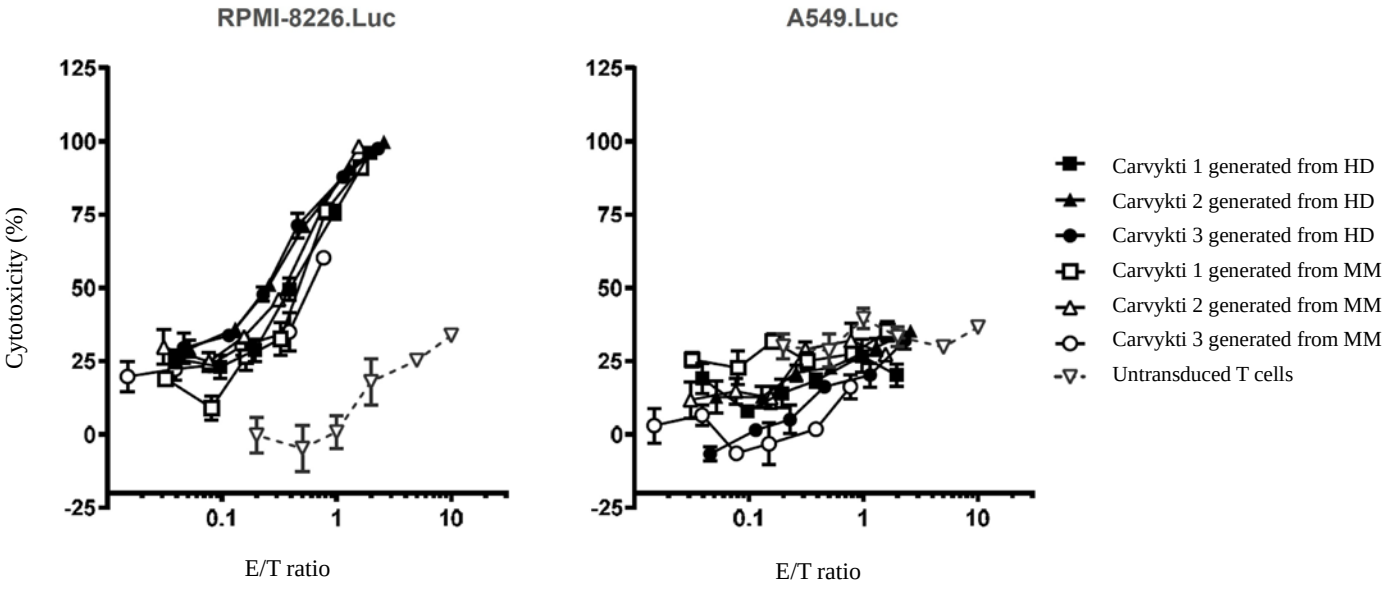

Figure 1. Carvykti cytotoxicity against BCMA-positive target cells

[4] Submitted as reference data.
[5] A recombinant protein containing the BCMA-binding domain of Carvykti with a His-tag at its C-terminus
[6] RPMI8226 human MM cells stably expressing the firefly luciferase gene
[7] A549 human lung adenocarcinoma cells stably expressing the firefly luciferase gene

3.1.3 BCMA-dependent cytokine release induced by Carvykti (CTD 4.2.1.1.16)

Carvykti generated from a healthy donor, Carvykti generated from a MM patient, or untransduced T cells generated from a healthy donor as a negative control were co-cultured with the target cells (RPMI8226.Luc cells or A549.Luc cells) [see Section 3.1.2]. IFN-γ release from effector cells was assayed by an enzyme-linked immunosorbent assay (ELISA). Carvykti did not elicit IFN-γ release when co-cultured with A549.Luc cells with no BCMA expression, but showed an E/T ratio-dependent IFN-γ release with BCMA-expressing RPMI8226.Luc cells. On the other hand, co-culture of these cells with untransduced T cells did not lead to increased IFN-γ production (Figure 2).

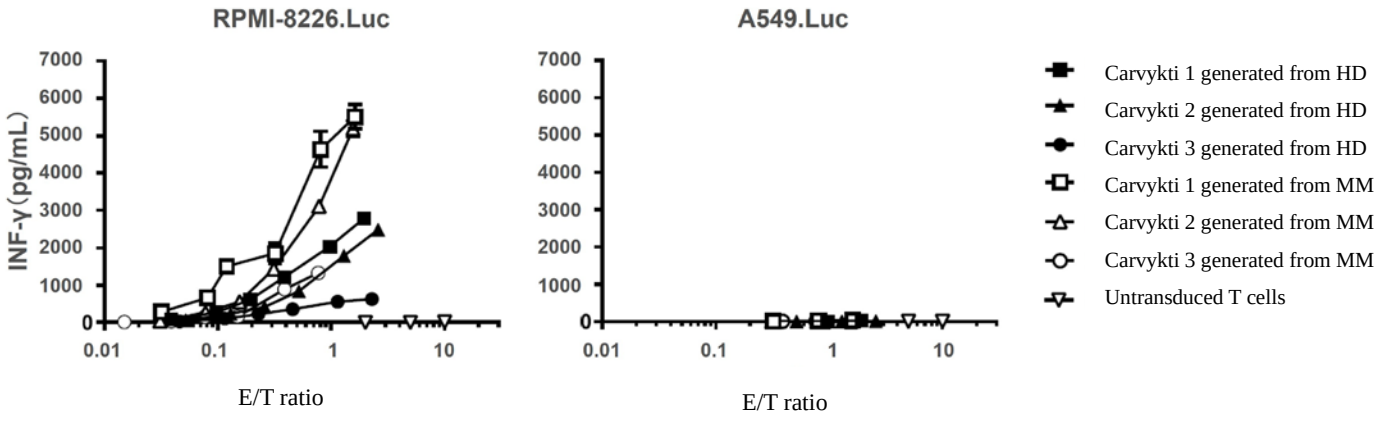

Figure 2. BCMA-dependent IFN-γ release induced by Carvykti

3.2 *In vivo* studies

3.2.1 Assessment of pharmacological activity of Carvykti in NCG mice intravenously injected with human MM cell line (CTD 4.2.1.1.17[4])

Female NOD-Prkdc^{em26Cd52}Il2rgem26Cd22/Nju (NCG) mice were implanted by tail vein injection with 3.5×10^6 RPMI8226.Luc cells derived from human MM.[6] Upon tumor engraftment, the mice received a single intravenous dose of 4.0×10^6 cells of Carvykti generated from a MM patient or untransduced T cells generated from a MM patient as a negative control (n = 8/group). The day of administration of Carvykti or untransduced T cells was defined as Day 0, and the anti-tumor activity[8] and survival rate were evaluated for 98 days. Carvykti showed a statistically significant tumor inhibition compared with untransduced T cells ($P < 0.01$, Student's t-test). The median survival was 20 days in the untransduced T cells group and 45.5 days in the Carvykti group, showing an increase in the survival of animals in the Carvykti group. On Day 69, the surviving animals with disappeared tumors in the Carvykti group were re-injected via tail vein with 0.75×10^6 RPMI8226.Luc cells derived from human MM. No increase in tumor growth was observed in the surviving animals following tumor re-challenge.

[8] Using bioluminescence imaging, anti-tumor activity was evaluated by measuring the luciferase activity of RPMI8226.Luc cells as the emission intensity.

3.2.2 Assessment of dose-dependent anti-tumor efficacy of Carvykti in NCG mice intravenously injected with human MM cell line (CTD 4.2.1.1.18[4])

Male and female NCG mice were implanted by tail vein injection with 4.0×10^6 RPMI8226.Luc cells derived from human MM.[6] Upon tumor engraftment, the mice received a single intravenous dose of normal saline (vehicle), Carvykti generated from a healthy donor (1.3×10^5, 6.6×10^5, or 3.3×10^6 cells [2.46×10^4, 1.251×10^5, or 6.257×10^5 CAR-positive T cells]), Carvykti generated from a MM patient (1.3×10^5, 6.6×10^5, or 3.3×10^6 cells [2.61×10^4, 1.327×10^5, or 6.633×10^5 CAR-positive T cells]), or untransduced T cells generated from a MM patient as a negative control (1.3×10^5, 6.6×10^5, or 3.3×10^6 cells) (n = 6/group). The day of administration was defined as Day 0, and the anti-tumor activity,[8] body weights over time, and survival rate were evaluated for 62 days. Carvykti generated from a healthy donor and Carvykti generated from a MM patient at a dose of 3.3×10^6 cells showed significant tumor inhibition compared with untransduced T cells at the same dose ($P < 0.01$, Student's t-test). In addition, Carvykti generated from a healthy donor and Carvykti generated from a MM patient at a dose of 3.3×10^6 cells showed increased survival[9] compared with Carvykti at lower doses, normal saline, and untransduced T cells. A dose-response relationship was observed for anti-tumor activity and survival rate. While decreases in body weight were observed in the normal saline group or the untransduced T cells group, body weights remained stable for mice dosed with 6.6×10^5 or 3.3×10^6 cells of Carvykti generated from a healthy donor or Carvykti generated from a MM patient.

3.R Outline of the Review Conducted by PMDA

The applicant's explanation about the efficacy of Carvykti:

In vitro studies demonstrated that Carvykti exhibits BCMA-specific IFN-γ release and cytotoxicity. In *in vivo* studies, a single intravenous dose of Carvykti showed tumor inhibition and increased survival in mice engrafted with BCMA-expressing human MM cell line.

The above results indicate that upon recognition of BCMA-expressing MM cells, Carvykti exerts cytotoxic effects.

PMDA accepted the applicant's explanation.

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

The applicant submitted the following data as a non-clinical pharmacokinetic study of Carvykti.

4.1 Evaluation of expansion and persistence of Carvykti in NCG mice intravenously injected with human MM cell line (CTD 4.2.1.1.18[4])

NCG mice were implanted by tail vein injection with RPMI8226.Luc cells derived from human MM and received a single intravenous dose of up to 3.3×10^6 cells of Carvykti [see Section 3.2.2]. The day of

[9] On Day 62, all mice dosed with 3.3×10^6 cells of Carvykti generated from a healthy donor or Carvykti generated from a MM patient survived, whereas there were no surviving mice in the lower doses (1.3×10^5 and 6.6×10^5 cells), normal saline, and untransduced T cells groups, except for 2 mice dosed with 6.6×10^5 cells.

administration was defined as Day 0. CAR gene copy number in mouse blood samples on Days −8, 6, 20, 34, and 48 were quantified by a quantitative polymerase chain reaction (qPCR) assay, and the expansion and persistence of Carvykti were evaluated. In both the Carvykti generated from a healthy donor and Carvykti generated from a MM patient groups, CAR gene copy number showed increases after Day 20 and peaked on Day 34, followed by decreases to baseline levels on Day 48.

4.R Outline of the Review Conducted by PMDA

Based on the submitted data, PMDA accepted the applicant's explanation about the non-clinical pharmacokinetics of Carvykti.

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

The applicant submitted non-clinical safety data in the form of the results of lentiviral vector integration site analysis, *in vitro* IL-2-dependent cellular proliferation analysis, assessment of the binding specificity of Carvykti in a human membrane surface protein array, assessment of off-target binding to Claudin-9 using cells, and safety assessment of impurities and the excipient.

5.1 Assessment of general toxicity

Since Carvykti lacks cross-reactivity to rodent and non-human primate BCMA [see Section 3.1.1], there is no pharmacologically relevant animal species. Thus, off-target toxicity unrelated to pharmacological action was evaluated in a primary pharmacodynamic study in mice intravenously injected with human MM cell line.

5.1.1 Study of Carvykti in mice intravenously injected with human MM cell line (CTD 4.2.1.1.18[4])

NCG mice were implanted by tail vein injection with RPMI8226.Luc cells derived from human MM. A single dose of up to 3.3×10^6 cells of Carvykti was intravenously administered to the animals [see Section 3.2.2]. The survival rate, clinical signs, and body weights were evaluated. There was no evident toxicity related to Carvykti.

5.1.2 Assessment of off-target binding

5.1.2.1 Assessment of binding specificity of Carvykti in a human membrane surface protein array (CTD 4.2.1.1.7[4])

The binding of Carvykti to 5,647 human membrane proteins expressed in HEK293 cells was assessed in an *in vitro* human membrane surface protein array. BCMA and claudin-9 were identified to bind to Carvykti.

5.1.2.2 Assessment of off-target binding to Claudin-9 using cells (CTD 4.2.1.1.10[4])

Binding of Carvykti to Claudin-9 was detected in a human membrane surface protein array [see Section 5.1.2.1]. The potential binding of Carvykti to Claudin-9 in engineered cell lines and primary cells was assessed (Table 11).

Table 11. Assessment of off-target binding to Claudin-9 using cells

Cells used	Test method	Results
• HEK293 cells that were engineered to express Claudin-9[*1] • Human MM H929 cells that were engineered to express Claudin-9[*2] • Cells that endogenously express Claudin-9 (primary peripheral blood monocytes and mDC)	The binding of Carvykti and LAB003-His[*3] to these cells was assessed by flow cytometry.	• Both Carvykti and LAB003-His bind to the cell lines that were engineered to express Claudin-9. • Neither Carvykti nor LAB003-His bind to the cells that endogenously express Claudin-9.

*1 No BCMA expression
*2 As H929 cells endogenously express BCMA, BCMA knockout H929 cell line that was engineered to express Claudin-9 was prepared.
*3 A recombinant protein containing the BCMA-binding domain of Carvykti with a His-tag at its C-terminus

The applicant's explanation about the above findings:

Given the following points, Carvykti is unlikely to bind to endogenously expressed human Claudin-9.

- Human MM H929 cells that were engineered to express Claudin-9 and primary peripheral blood monocytes express comparable levels of Claudin-9. The difference in the binding of Carvykti and LAB003-His between exogenously and endogenously expressed Claudin-9 is not considered attributable to differences in the level of Claudin-9 expression.
- Exogenously expressed protein on human cell line and endogenously expressed protein on primary human cells may have different post-translational modifications, possibly resulting in a difference in binding.

5.2 Assessment of tumorigenic and oncogenic potential

The risk of insertional oncogenicity resulting from the lentiviral vector integration into the chromosome was evaluated by lentiviral vector integration site analysis and *in vitro* IL-2-dependent cellular proliferation analysis. The applicant explained that the lentiviral vector to be used to generate Carvykti lacks the enhancer and promoter sequences in the LTR and is therefore unlikely to activate the genes in the proximity of the integration site.

5.2.1 Lentiviral vector integration site analysis (CTD 4.2.3.3.1.1[4])

Deep sequencing and shearing extension primer tag selection/ligation-mediated PCR were used to determine the integration site of the lentiviral vector (Table 12). According to the applicant's explanation, the analytical data suggested no risk of insertional oncogenicity resulting from the lentiviral vector integration into the T cell genome.

Table 12. Lentiviral vector integration site analysis

Test system and test method	Results
Genomic DNA isolated from Carvykti underwent deep sequencing and shearing extension primer tag selection/ligation-mediated PCR to identify the insertion sequence and site.	• Samples showed a highly polyclonal integration profile, and single clones with elevated frequencies in proximity to cancer-associated genes were not observed. • The integration patterns were similar to those reported for the wild-type lentivirus (integration into gene-rich regions, CpG islands, DNase I hypersensitive site, and GC-rich region).

5.2.2 *In vitro* IL-2-dependent cellular proliferation analysis (CTD 4.2.3.7.7.1[4])

Carvykti was cultured in the presence or absence of IL-2 in an *in vitro* growth assay (Table 13). There was no evidence for IL-2 independent T cell proliferation, suggesting no risk for oncogenic transformation of Carvykti.

Table 13. *In vitro* IL-2-dependent cellular proliferation analysis

Test system and test method	Results
Carvykti was cultured in the presence or absence of IL-2, and the cell counts etc. were evaluated up to 39 days.	The cells tended to proliferate in the presence of IL-2. On the other hand, the cell count decreased over time after Day 7, in the absence of IL-2.

5.3 Safety assessment of impurities

Safety assessment of process-related impurities that may be present in the final product was conducted based on non-clinical data, clinical experience, physiological concentrations, etc., taking account of the estimated residual levels of these impurities in the clinical dose of Carvykti. The applicant considers that these impurities pose little safety concern in humans.

5.4 Safety assessment of excipient

The excipient contained in Carvykti is the cryoprotectant (CryoStor CS5). In view of the content of the excipient in the clinical dose of Carvykti, safety assessment of CryoStor CS5 was conducted based on clinical experience and other information. The applicant considers that CryoStor CS5 poses little safety concern in humans.

5.R Outline of the Review Conducted by PMDA

Based on the presented data and the considerations shown in the following subsections, PMDA concluded that there are no particular concerns about the non-clinical safety of Carvykti.

5.R.1 Reproductive and developmental toxicity

The applicant's explanation about whether there is any effect of Carvykti on fetuses and infants if Carvykti is administered to pregnant women or women become pregnant following treatment with Carvykti:

The expression of BCMA in normal human tissues is restricted to B cells, plasmablasts, and plasma cells (*Blood*. 2007; 109: 729-39, *J Clin Invest*. 2003; 112: 286-97). BCMA expression in human tissues was assessed by immunohistochemistry with anti-BCMA polyclonal antibody, and the results did not show any evidence suggesting binding to male or female reproductive organs (*Clin Cancer Res*. 2013; 19: 2048-60). Assessment of the off-target binding of Carvykti [see Section 5.1.2] also showed the binding specificity of Carvykti to the target antigen and did not raise any concern about off-target toxicity.

On the other hand, given the mechanism of action of Carvykti and the expression profile of BCMA in plasma cells and mature B-cell subset, the fetus may have B lymphocytopenia and humoral immune defect if CAR-positive T cells cross the placenta. Thus, using the package insert, women of childbearing potential will be advised to use contraception during treatment with Carvykti and for a certain period of time after treatment with Carvykti. As of the data cutoff date of February 24, 2022, no pregnant patients who received Carvykti or pregnancies after Carvykti therapy have been reported.

PMDA's view:

The applicant's explanation has been accepted. However, because the currently available information on the

reproductive and developmental toxicity of Carvykti is very limited, the applicant should collect information on fetal effects if pregnant women treated with Carvykti are identified in the post-marketing setting.

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

Based on the data obtained from Study MMY2001, the clinical pharmacokinetics of Carvykti were characterized.

6.1 Study MMY2001 (CTD 5.3.5.2.1[10])

6.1.1 Assessment of blood CAR transgene levels

Blood CAR transgene levels over time were measured in 97 non-Japanese subjects (29 in the phase Ib part, 68 in the phase II part) and 9 Japanese subjects in the phase II part in Study MMY2001.

In Study MMY2001, Carvykti was administered as a single intravenous infusion at a target dose of 0.75×10^6 CAR-positive viable T cells/kg to patients with relapsed or refractory MM. Blood CAR transgene levels were measured by qPCR assay, using blood samples collected at pre-dose, on the day of Carvykti infusion, and at 2, 3, 7, 10, 14, 21, 28, 42, 56, 78, and 100 days post-infusion and then every 4 weeks up to approximately 1 year post-infusion.

The median times to reach peak levels of blood CAR transgene were 12.7 and 12.9 days post-infusion in the non-Japanese and Japanese populations, respectively, and then blood CAR transgene levels declined (Figure 3). Table 14 shows CAR transgene PK parameters. The mean blood CAR transgene C_{max}, $AUC_{0\text{-}28d}$, and $t_{1/2}$ in the non-Japanese population were similar to those in the Japanese population. On the other hand, high inter-individual variability was observed for all PK parameters.

[10] Although the clinical study report (CSR) for the non-Japanese population included the results of analysis of the data as of the data cutoff date of [redacted], 20[redacted], programming errors concerning the handling of the limit of quantification for blood CAR transgene were found after the issuance of the CSR. This section presents the results of additional analysis of the data as of the data cutoff date of February 11, 2021 performed after the resolution of the programming errors.

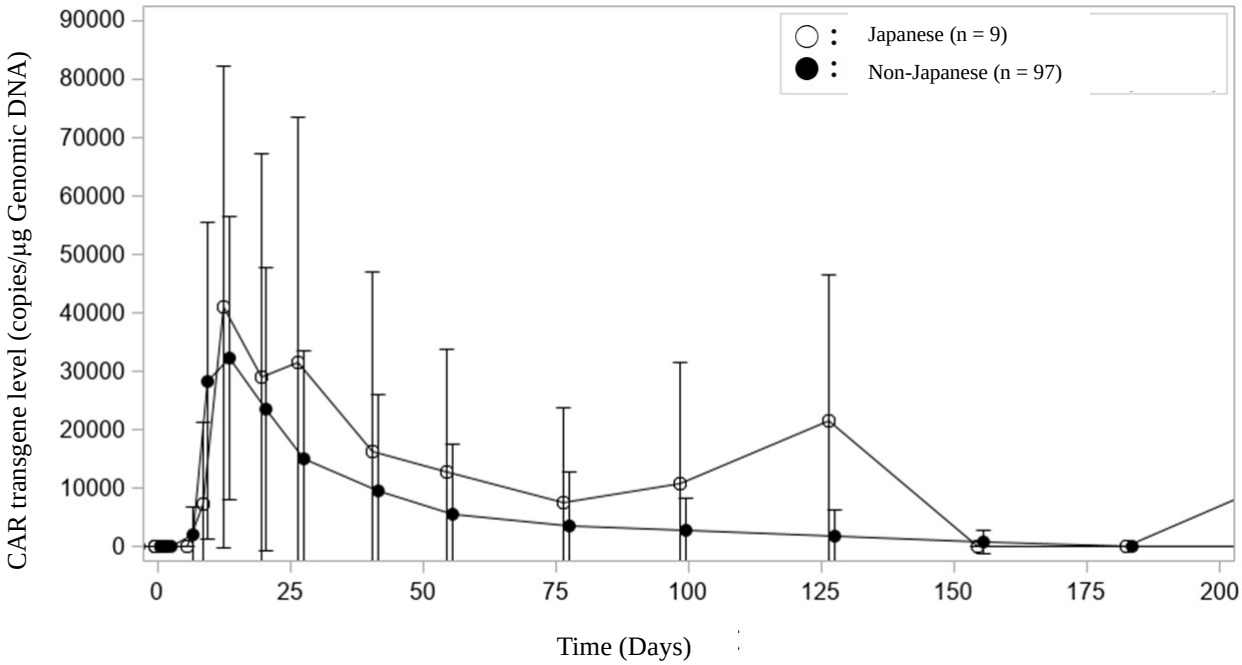

Figure 3. Blood CAR transgene levels over time in Study MMY2001 (Mean ± SD)

Table 14. CAR transgene PK parameters in Study MMY2001

PK parameters	Japanese N = 9[*3]	Non-Japanese N = 97[*4]	Japanese + Non-Japanese N = 106[*5]
C_{max}[*1] (copies/µg)	44,077 (39,911)	48,692 (27,174)	48,301 (28,252)
t_{max}[*2] (days)	12.87 (8.72-13.84)	12.71 (8.73-329.77)	12.75 (8.72-329.77)
C_{last}[*1] (copies/µg)	7,549 (13,852)	2,874 (8,462)	3,271 (9,044)
t_{last}[*2] (days)	129.89 (24.97-324.88)	125.90 (20.04-702.12)	126.30 (20.04-702.12)
t_{bql}[*2] (days)	96.87 (19.73-157.86)	99.98 (27.89-364.73)	99.97 (19.73-364.73)
$AUC_{0\text{-}28d}$[*1] (day·copies/µg)	592,118 (7,473,95)	504,496 (385,380)	511,935 (423,025)
$AUC_{0\text{-}6m}$[*1] (day·copies/µg)	2,295,832 (3,810,335)	1,033,373 (1,355,394)	1,141,584 (1,709,104)
AUC_{last}[*1] (day·copies/µg)	2,921,598 (5,219,114)	1,098,030 (1,387,010)	1,252,861 (2,023,634)
$t_{1/2}$[*1] (days)	22.2 (17.6)	23.5 (24.2)	23.4 (23.7)

*1 Mean (SD)

*2 Median (range)

*3 N = 7 for t_{bql}, N = 3 for $t_{1/2}$

*4 N = 96 for $AUC_{0\text{-}6m}$, N = 65 for t_{bql}, N = 42 for $t_{1/2}$

*5 N = 105 for $AUC_{0\text{-}6m}$, N = 72 for t_{bql}, N = 45 for $t_{1/2}$

The applicant's explanation about the exposure-efficacy and exposure-safety relationships:

The exposure-efficacy relationship was evaluated based on blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$. Within the observed exposure range, 3 subjects did not achieve a partial response (PR) or better (0 in the Japanese population), and 103 subjects (including all 9 subjects in the Japanese population) were responders. Thes results precluded drawing a conclusion on the exposure-efficacy relationship.

The exposure-safety relationship was evaluated based on blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$. Blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher in subjects with cytokine release syndrome (CRS), immune effector

cell-associated neurotoxicity syndrome (ICANS), other neurotoxicities (including movement and neurocognitive adverse events), or movement and neurocognitive adverse events than in subjects without these events. However, blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$ values across adverse event categories overlapped between subjects with and without these adverse events. The limited number of subjects with Grade ≥3 CRS (5 subjects) (0 in the Japanese population) or Grade ≥3 ICANS (2 subjects) (0 in the Japanese population) precluded drawing a definitive conclusion on the exposure-safety relationship.

6.1.2 Assessment of anti-Carvykti antibodies

Anti-Carvykti antibody titers were measured in 97 non-Japanese subjects (29 in the phase Ib part, 68 in the phase II part) and 9 Japanese subjects in the phase II part in Study MMY2001. By the data cutoff date, 19 of the 97 subjects (19.6%) in the non-Japanese population and 2 of the 9 subjects (22.2%) in the Japanese population tested positive for anti-Carvykti antibodies.[11)]

The applicant's explanation about the impact of anti-Carvykti antibodies on the PK, efficacy, and safety of Carvykti:

- Blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were shown to be similar between antibody-positive and antibody-negative subjects.
- The majority of subjects treated with Carvykti were responders, and all of subjects who were antibody-positive as of the data cutoff date were responders. Thus, there was no clear association between the incidence or titer of anti-Carvykti antibodies and the clinical efficacy of Carvykti.
- The incidences of CRS, ICANS, and other neurotoxicities (including movement and neurocognitive adverse events) were similar between antibody-positive and antibody-negative subjects, and no movement and neurocognitive adverse events were reported in antibody-positive subjects. There was no clear association between those adverse events and anti-Carvykti antibodies.

6.R Outline of the Review Conducted by PMDA

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

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 1 global phase Ib/II study presented in Table 15.

[11)] Antibody-positive subjects were defined as those with a rise in antibody titer during the study.

Table 15. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of patients enrolled	Dosing regimen	Main endpoints
Evaluation	Global	MMY2001	Ib/II	Patients with relapsed or refractory MM	Phase Ib part: 35 Phase II part Main cohort: 78 Japanese cohort: 13	A single intravenous infusion of 0.75×10^6 anti-BCMA CAR-positive viable T cells/kg (range, $0.5\text{-}1.0 \times 10^6$ cells/kg)	Efficacy Safety

The clinical study is summarized below. The most common adverse events other than deaths reported in the clinical study are presented in Section "9. Adverse Events Reported in Clinical Studies."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase Ib/II study (CTD 5.3.5.2.1, Study MMY2001 [ongoing since July 2018 (data cutoff date of July 22, 2021)])

An open-label, uncontrolled study was conducted at 21 sites in the US and Japan (4 sites in Japan) to evaluate the efficacy and safety of Carvykti in patients with relapsed or refractory MM (target sample size, 24-50 subjects in the phase Ib part, 60 subjects in the main cohort of the phase II part, 8 subjects in the Japanese cohort of the phase II part). Table 16 shows key inclusion/exclusion criteria.

Table 16. Key inclusion/exclusion criteria

Inclusion criteria
- Patients with relapsed or refractory MM ≥18 years of age (≥20 years of age in Japan) who:
  - Received at least 3 prior MM treatment lines of therapy (induction with or without haematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen), or are double refractory to an immunomodulatory drug and a proteasome inhibitor.
  - Had at least 1 complete cycle of treatment for each regimen, unless PD was the best response.
  - Received prior therapy with an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody.
  - Have documented disease progression on or within 12 months of the most recent therapy. Subjects with documented disease progression within the previous 6 months and who are refractory or non-responsive to their most recent line of therapy afterwards are eligible.
- Measurable disease as defined by any of the following:
  - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 h
  - FLC ≥10 mg/dL (100 mg/L) and abnormal serum FLC ratio determined using serum FLC assay
- ECOG PS of 0 or 1

Exclusion criteria
- Prior treatment with CAR-T therapy directed at any target or any therapy that is targeted to BCMA.
- Received an allogenic stem cell transplant within 6 months before apheresis or an autologous stem cell transplant within12 weeks before apheresis.
- Have known active, or prior history of central nervous system (CNS) involvement, or clinical signs of meningeal involvement of multiple myeloma
- Plasma cell leukemia at the time of screening, Waldenström's macroglobulinaemia, POEMS syndrome, or primary AL amyloidosis

The study was comprised of 2 parts: phase Ib and phase II parts. The phase II part included the main cohort to evaluate the efficacy and safety of Carvykti in non-Japanese patients and the Japanese cohort to evaluate the efficacy and safety of Carvykti in Japanese patients. Each part consisted of screening, leukapheresis, lymphodepleting (LD) chemotherapy, Carvykti infusion, and follow-up (post-infusion follow-up [from Day 1 to Day 100] and post-treatment follow-up [from Day 101 to the day of study completion[12)]]).

Carvykti was to be administered as a single intravenous infusion at a target dose of 0.75×10^6 anti-BCMA CAR-positive viable T cells/kg (range, $0.5\text{-}1.0 \times 10^6$ CAR-positive viable T cells/kg with a maximum of $1.0 \times$

[12)] Two years after the last subject received his/her initial dose of Carvykti.

10^8 CAR-positive viable T cells). Subjects could be considered for retreatment with Carvykti at the target dose of 0.75×10^6 anti-BCMA CAR-positive viable T cells/kg (or at a de-escalated dose if needed) if all of the following criteria were met:

- PD after the best response of minimal response (MR) or better.
- No ongoing Grade ≥3 haematologic toxicity.
- No ongoing Grade ≥2 non-haematologic toxicity (with the exception of nausea, vomiting, hair loss, and constipation).
- At least 6 months between the first Carvykti infusion and detection of PD.

The LD chemotherapy regimen of intravenous cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 doses was to be administered to help promote CAR-T cell engraftment and expansion, and Carvykti infusion was to occur 5 to 7 days after the start of the LD chemotherapy. Subjects could receive bridging therapy between leukapheresis and the initiation of the LD chemotherapy if clinically indicated to maintain disease stability. Bridging therapy must have been a short-term treatment which previously generated at least a response of stable disease (SD) for the subject. Prior anti-tumor therapy within the specified timeframe prior to leukapheresis and LD chemotherapy was prohibited.[13)]

The target sample size for the study was determined to establish a recommended dose level and assess the safety of Carvykti, and a minimum of 24[14)] and up to 50 subjects in the phase Ib part were planned to receive Carvykti. With 60 subjects in the main cohort of the phase II part, the study would achieve approximately 90% power to test the null hypothesis that the overall response rate (ORR) is 30%[15)] vs. the alternative hypothesis that the ORR is 50% at a one-sided alpha level of 0.025.

In the phase Ib part and the main cohort of the phase II part for a non-Japanese patient population, 113 subjects (35 in the phase Ib part, 78 in the phase II part) were enrolled, all of whom underwent leukapheresis. Prior to the LD chemotherapy, 12 subjects were withdrawn from the study (PD [2 subjects], consent withdrawal [2 subjects], and death [8 subjects]). Prior to Carvykti infusion, 4 subjects who received the LD chemotherapy were withdrawn from the study (consent withdrawal [3 subjects] and death [1 subject]). The remaining 97 subjects who received Carvykti (29 in the phase Ib part, 68 in the phase II part) constituted the primary efficacy and safety analysis sets. Thirteen subjects were included in the Japanese cohort, all of whom underwent leukapheresis. Prior to LD chemotherapy, 4 subjects were withdrawn from the study (PD [2 subjects], an adverse event [1 subject], and consent withdrawal [1 subject]). Among the 9 subjects who received Carvykti,

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13) (1) Targeted therapy, epigenetic therapy, or treatment with an investigational drug, or an invasive investigational medical device within 14 days or at least 5 half-lives, whichever is less.
(2) Monoclonal antibody treatment for MM within 21 days.
(3) Cytotoxic therapy within 14 days.
(4) Proteasome inhibitor therapy within 14 days.
(5) Immunomodulatory agent therapy within 7 days.
(6) Radiotherapy within 14 days. However, if the radiation portal covered ≤5% of the bone marrow reserve, the subject was eligible irrespective of the end date of radiotherapy.

14) With 24 treated subjects, if the true incidence rate of adverse events identified as potential risks (e.g., CRS) was 10%, the probability of detecting at least 1 subject experiencing the event would exceed 90%.

15) At the time of planning the study, the reported overall response rate (the primary endpoint) for therapies available for patients with relapsed or refractory MM (including daratumumab) was ≤30% (*Lancet Oncol*. 2013; 14: 1055-66, *Leukemia*. 2017; 31: 107-14, etc.).

8 subjects were included in the efficacy analysis population. The remaining 1 subject who received Carvykti at a dose below the target dose range was excluded from the analysis. One non-Japanese patient received retreatment with Carvykti.

The primary efficacy endpoint for the study was the overall response rate according to the International Myeloma Working Group (IMWG) criteria (*Lancet Oncol.* 2016; 17: e328-46), as assessed by an Independent Response Committee (IRC). The non-Japanese population in the phase I part and the main cohort of the phase II part served as the primary population for efficacy evaluation.[16)]

Table 17 shows the results of the primary endpoint in the non-Japanese population as of the data cutoff date of September 1, 2020, i.e., ≥6 months after the last subject received Carvykti infusion. The overall response rate [95% confidence interval (CI)] was 96.9% [91.2%, 99.4%], which was greater than the threshold of 30%, demonstrating statistical significance.

Table 17. Best response according to IMWG criteria
(IRC assessment, Efficacy analysis population, data cutoff date of September 1, 2020)

	n (%)		
	Non-Japanese population		
	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
sCR	25 (86.2)	40 (58.8)	65 (67.0)
CR	0	0	0
VGPR	3 (10.3)	22 (32.4)	25 (25.8)
PR	1 (3.4)	3 (4.4)	4 (4.1)
MR	0	0	0
SD	0	0	0
PD	0	1 (1.5)	1 (1.0)
NE	0	2 (2.9)	2 (2.1)
Response (sCR, CR, VGPR, or PR)	29	65	94
Overall response rate (%)	100	95.6	96.9
[95% CI[*1]] (%)	[88.1, 100]	[87.6, 99.1]	[91.2, 99.4]
P-value (one-sided)[*2]			< 0.0001

*1: Clopper-Pearson method
*2: A one-sided exact binomial test with significance level of 0.025 for the null hypothesis of ORR ≤30%

Table 18 shows the results at ≥12 months after the last subject received Carvykti infusion (data cutoff date of July 22, 2021 for the Japanese population, data cutoff date of February 11, 2021 for the non-Japanese population). The overall response rate [95% CI] in 8 subjects in the Japanese population was 100% [63.1%, 100%].

16) The protocol and the statistical analysis plan pre-specified that the pooling of data from the phase Ib part and the main cohort of the phase II part for analysis is allowed if appropriate.

Table 18. Best response according to IMWG criteria
(IRC assessment, Efficacy analysis population,
data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

	n (%)			
	Japanese population	Non-Japanese population		
	N = 8	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
sCR	4 (50.0)	28 (96.6)	50 (73.5)	78 (80.4)
CR	0	0	0	0
VGPR	4 (50.0)	0	14 (20.6)	14 (14.4)
PR	0	1 (3.4)	2 (2.9)	3 (3.1)
MR	0	0	0	0
SD	0	0	0	0
PD	0	0	1 (1.5)	1 (1.0)
NE	0	0	1 (1.5)	1 (1.0)
Response (sCR, CR, VGPR, or PR)	8	29	66	95
Overall response rate (%)	100	100	97.1	97.9
[95% CI*] (%)	[63.1, 100]	[88.1, 100.0]	[89.8, 99.6]	[92.7, 99.7]

*: Clopper-Pearson method

Safety analysis (data cutoff date of February 11, 2021) showed that 21 subjects (all non-Japanese subjects) died after Carvykti infusion. All deaths occurred ≥31 days after Carvykti infusion. The causes of deaths were disease progression (10 subjects) and adverse events (11 subjects [acute myeloid leukaemia in 3 subjects; and lung abscess, sepsis, septic shock, CRS, neurotoxicity, respiratory failure, ascites, and pneumonia in 1 subject each]). A causal relationship to Carvykti could not be ruled out for 6 deaths due to adverse events (lung abscess,[17] sepsis,[18] septic shock,[19] CRS,[20] neurotoxicity,[21] and respiratory failure[22] in 1 subject each).

7.R Outline of the Review Conducted by PMDA

7.R.1 Efficacy

Based on the following considerations, PMDA concluded that a certain level of efficacy of Carvykti was demonstrated in patients with relapsed or refractory MM.

17) A 6[redacted]-year-old male patient. The patient had CRS (Grade 1) on Day 7 following Carvykti infusion and ICANS (Grade 1) on Day 8. CRS worsened to Grade 2, but both events resolved on Day 10. Parkinsonism (Grade 1) occurred on Day 19 and worsened to Grade 3 on Day 30. The patient had bacterial sepsis and skin infection (Grade 3) on Day 57. CT revealed chronic subdural haematoma on Day 52. The patient experienced somnolence (Grade 3) on Day 64 and was admitted to the ICU. The patient had pneumonia (Grade 3) on Day 72 and lung abscess on Day 119. The patient died on Day 119.

18) A 7[redacted]-year-old male patient. CRS (Grade 2) occurred on Day 2 following Carvykti infusion and resolved on Day 8. ICANS (Grade 3) occurred on Day 6 and worsened to Grade 4 on the following day, but resolved on Day 14. Mental status changes occurred on Day 17, and tendency to somnolence persisted. The patient had sepsis (Grade 4) on Day 40 and died on Day 45.

19) A 5[redacted]-year-old male patient. CRS (Grade 1) occurred on Day 9 following Carvykti infusion and worsened to Grade 2 on Day 11 and Grade 3 on Day 13. Parkinsonism (Grade 1) occurred on Day 101. The patient had septic shock on Day 161 and died on the following day.

20) A 7[redacted]-year-old male patient. CRS (Grade 1) occurred on Day 3 following Carvykti infusion and worsened to Grade 3 on Day 11 and Grade 4 on Day 13. The patient received methylprednisolone, etanercept, anakinra, cyclophosphamide, and tocilizumab to treat CRS, but died on Day 99. Autopsy revealed concurrent HLH, and the patient was determined to have died from CRS.

21) A 5[redacted]-year-old male patient. CRS (Grade 2) and ICANS (Grade 1) occurred on Day 8 following Carvykti infusion and resolved on Day 11. Parkinsonism (Grade 2) occurred on Day 43. Altered mental status (Grade 3) occurred on Day 100. Parkinsonism worsened to Grade 3 on Day 105. The patient had hallucination and became unresponsive on Day 246 and died from neurotoxicity on the following day.

22) A 6[redacted]-year-old female patient. CRS (Grade 1) and ICANS (Grade 2) occurred on Day 8 following Carvykti infusion and resolved on Day 9. CRS (Grade 1) and ICANS (Grade 1) occurred on Day 11 and resolved on Days 14 and 12, respectively. The patient had sepsis (Grade 3) on Day 88, abscess limb on Day 91, and neurotoxicity (Grade 4) and cerebellar infarction (Grade 2) on Day 93. The patient was treated with antibiotics, dexamethasone, anakinra, etc., but no improvement was observed. The patient had deep vein thrombosis (Grade 4) on Day 116 and pulmonary embolism on Day 121 The patient died from respiratory failure on Day 121.

7.R.1.1 Method of efficacy assessment

The applicant's explanation about (a) the reason for selecting the overall response rate as the primary endpoint and (b) the reason for pooling the data from the phase Ib and II parts for assessment in Study MMY2001:

(a) The reason for selecting the overall response rate as the primary endpoint

A reduction in clinical symptoms of tumors (bone pain, anaemia, renal insufficiency, etc.) is expected to be shown in responders. Increases in progression-free survival (PFS) and overall survival (OS) resulting from delayed relapse (disease progression) are also expected. To this end, the overall response rate was selected as the primary endpoint for Study MMY2001.

(b) The reason for pooling the data from the phase Ib and II parts for assessment

Although a pooled analysis was not pre-defined as the primary analysis, the protocol and the statistical analysis plan pre-specified that the pooling of data from the phase Ib and phase II parts for analysis is allowed if appropriate. Because the inclusion criteria, the dosing regimen of Carvykti, the efficacy and safety assessment schedule, and other study designs were consistent between the phase Ib and II parts, the applicant considered that efficacy and safety analyses would not be affected by pooling the data, and then performed a pooled analysis.

PMDA's view:

The applicant's explanation about the overall response rate selected as the primary endpoint is understandable. However, the results of duration of response (DOR), PFS, and OS are also important for assessing the treatment effect in patients with relapsed or refractory MM. To evaluate the efficacy of Carvykti, a primary focus will be placed on the overall response rate, and then the results of DOR, PFS, and OS will also be reviewed.

When an assessment of the pooled data is performed, differences in the objectives of the phase Ib and II parts of the study may result in systematic differences in subject characteristics between these parts. Whether the data from these parts can be pooled for assessment needs to be determined carefully. Taking also into account that Study MMY2001 was an open-label, uncontrolled study, the applicant could have made a decision on whether to perform a pooled analysis based on the results of the ongoing study because the protocol and statistical analysis plan pre-specified that a pooled analysis may be performed as the primary analysis. Thus, this provision was not appropriate. However, since the results as presented in Table 17 showed no major differences in the primary endpoint of the overall response rate between the parts, the efficacy of Carvykti can be assessed based on the pooled data from the phase Ib and II parts of Study MMY2001.

7.R.1.2 Results of efficacy assessment

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

In Study MMY2001, the primary efficacy endpoint of the overall response rate according to the IMWG criteria as assessed by the IRC in the non-Japanese population [95% CI] was 96.9% [91.2%, 99.4%], which was greater than the pre-specified threshold of 30% (data cutoff date of September 1, 2020).

The median DOR in 95 responders in the non-Japanese population [95% CI] (months) as of the data cutoff date of February 11, 2021 was 21.8 [21.8, not estimable (NE)]. The estimated percentage of subjects with a response duration of ≥12 months [95% CI] was 72.9% [62.6%, 80.9%].

The median PFS in the non-Japanese population [95% CI] (months) as of the data cutoff date of February 11, 2021 was 22.8 [22.8, NE]. The estimated 12-month PFS rate [95% CI] was 76.3% [66.5%, 83.6%].

The median OS in the non-Japanese population [95% CI] (months) as of the data cutoff date of February 11, 2021 was not estimable due to insufficient events accured. The estimated 12-month OS rate [95% CI] was 87.6% [79.2%, 92.8%].

In 8 subjects in the Japanese population of Study MMY2001 (data cutoff date of July 22, 2021), the overall response rate [95% CI] was 100% [63.1%, 100%], which was not clearly different from that in the non-Japanese population.

Figure 4 shows treatment response over time by subject in the Japanese population. The median DOR [95% CI] (months) was not estimable [10.3, NE], and 6 subjects had a response duration of ≥12 months. The median PFS [95% CI] (months) was not estimable [11.17, NE], and the median OS [95% CI] (months) was not estimable [NE, NE].

The above results suggested durable responses in the Japanese population as in the non-Japanese population, indicating that Carvykti is expected to be effective in Japanese patients.

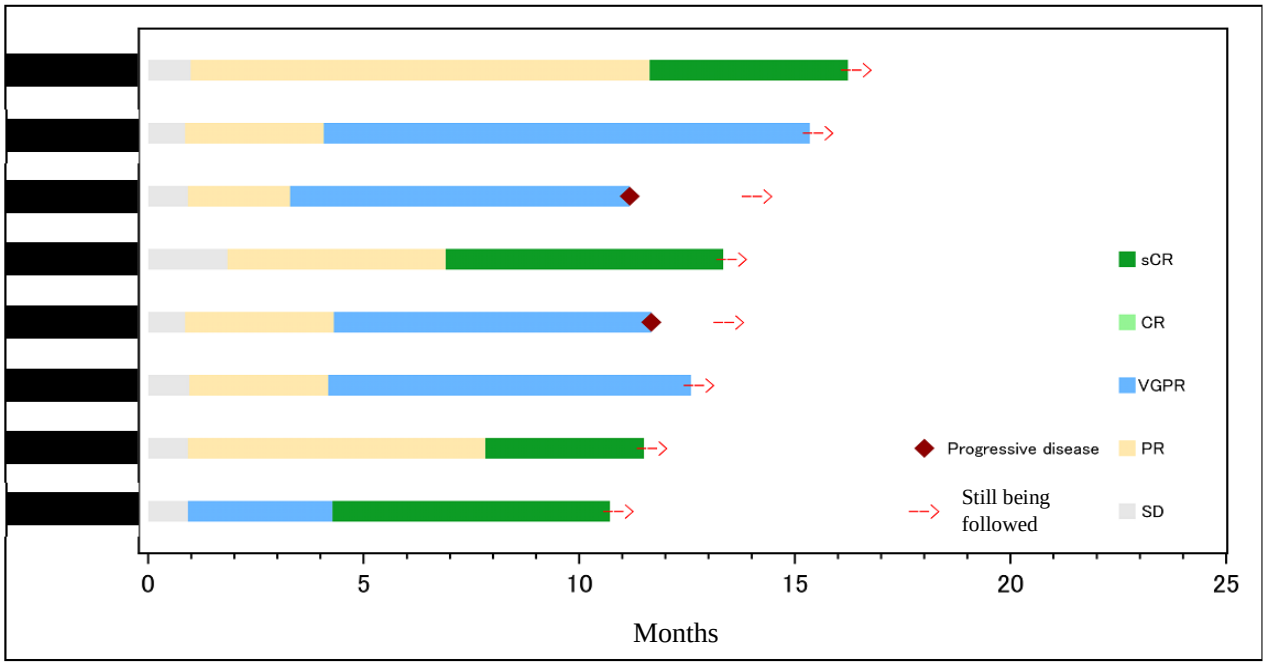

Figure 4. Swimmer's plot in Japanese population of Study MMY2001 (Efficacy analysis population, data cutoff date of July 22, 2021)

Furthermore, the efficacy of Carvykti was evaluated by comparison to an external control arm. The results are shown below.

A cohort of patients who met the key eligibility criteria for Study MMY2001 (patients meeting criteria for plasma cell leukemia and with no abnormalities in the renal function, who received subsequent treatment after becoming refractory to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody) were identified as the MAMMOTH cohort, from the data from the MAMMOTH study that investigated the outcomes of currently available treatments in patients with MM refractory to anti-CD38 monoclonal antibodies (*Leukemia*. 2019; 33: 2266-75). A comparison was made between the MAMMOTH cohort and the CARTITUDE-1 cohort (a population of non-Japanese patients who underwent leukapheresis in Study MMY2001).[23)] The overall response rates in the CARTITUDE-1 cohort (107 patients) and the MAMMOTH cohort (177 patients) were 83% and 34%, respectively, the 12-month PFS rates were 71% and 12%, respectively, and the 12-month OS rates were 81% and 42%, respectively. Better outcomes were observed in the CARTITUDE-1 cohort compared with the MAMMOTH cohort. Although there are limitations to comparison to an external control arm, the results of Study MMY2001 suggested the efficacy of Carvykti.

PMDA's view:
The above explanation by the applicant is understandable, and the results of Study MMY2001 demonstrated a certain level of efficacy of Carvykti in patients with relapsed or refractory MM.

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

PMDA's view:
Based on the following considerations, adverse events that require particular attention following Carvykti infusion are CRS, hemophagocytic lymphohistiocytosis (HLH), neurologic disorders, infections, cytopenia, hypersensitivity, hypogammaglobulinaemia, and tumor lysis syndrome (TLS). Patients should be monitored for signs and symptoms of these adverse events following Carvykti infusion.

Carvykti is tolerable as long as physicians with adequate knowledge of and experience in the treatment of MM take appropriate measures, such as monitoring for and management of adverse events, at medical institutions with adequate facilities for the management of the above adverse events.

7.R.2.1 Safety profile of Carvykti and differences between Japanese and non-Japanese populations

The applicant's explanation about the safety of Carvykti:

[23)] In order to assure comparability, a propensity score-based weighted analysis and a propensity score-based matching analysis were performed to account for important covariates affecting treatment outcomes in patients with MM. A propensity score-based weighted analysis was also restricted to the subset of patients with overlapping propensity scores.

Safety data from Study MMY2001 (data cutoff date of February 11, 2021 for the non-Japanese population, data cutoff date of July 22, 2021 for the Japanese population) are summarized in Table 19.[24)] No patients were admitted to the ICU twice or more after Carvykti infusion.

Table 19. Summary of safety data
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

	n (%)			
	Japanese population	Non-Japanese population		
	N = 9	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
All adverse events	9 (100)	29 (100)	68 (100)	97 (100)
Grade ≥3 adverse events	8 (88.9)	29 (100)	68 (100)	97 (100)
Serious adverse events	1 (11.1)	11 (37.9)	42 (61.8)	53 (54.6)
Death	0	6 (20.7)	15 (22.1)	21 (21.6)
Adverse events leading to death	0	4 (13.8)	7 (10.3)	11 (11.3)
ICU admission	0	0	4 (5.9)	4 (4.1)
Adverse events requiring ICU admission	0	0	4 (5.9)	4 (4.1)

The incidence of serious adverse events is shown in Section "9.1 Global phase Ib/II study (Study MMY2001)."

The applicant's explanation about differences in the safety of Carvykti between Japanese and non-Japanese populations:

Table 20 shows adverse events of any grade or Grade ≥3 adverse events reported at a ≥10% higher incidence in the Japanese population than in the entire non-Japanese population, and serious adverse events reported at a ≥5% higher incidence in the Japanese population than in the entire non-Japanese population.

[24)] Data on all adverse events occurring up to 100 days after Carvykti infusion or the start of subsequent anti-cancer therapy, whichever was earlier, all secondary malignancies observed during the study period, and events associated with HBV reactivation and neurologic events reported during the first year after Carvykti infusion were collected. Among all adverse events, data on those related to Carvykti were to be collected until the end of the study (2 years after the last subject received Carvykti infusion), and data on secondary malignancies were to be collected for 15 years after Carvykti infusion (yearly). In addition, adverse events observed after retreatment with Carvykti were also collected.

Table 20. Adverse events of any grade or Grade ≥3 adverse events reported at a ≥10% higher incidence in the Japanese population than in the entire non-Japanese population, and serious adverse events reported at a ≥5% higher incidence in the Japanese population than in the entire non-Japanese population
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

PT (MedDRA/J ver.23.0)	n (%)	
	Japanese population N = 9	Entire non-Japanese population N = 97
Adverse events of any grade		
Febrile neutropenia	3 (33.3)	10 (10.3)
Hypofibrinogenaemia	2 (22.2)	11 (11.3)
Lymphocytosis	2 (22.2)	1 (1.0)
Vomiting	3 (33.3)	19 (19.6)
Headache	3 (33.3)	19 (19.6)
Bacteraemia	1 (11.1)	1 (1.0)
Somnolence	1 (11.1)	1 (1.0)
Fluid retention	1 (11.1)	0
Embolism	1 (11.1)	0
Grade ≥3 adverse events		
Thrombocytopenia	7 (77.8)	58 (59.8)
Febrile neutropenia	3 (33.3)	9 (9.3)
Aspartate aminotransferase increased	3 (33.3)	5 (5.2)
Hypofibrinogenaemia	2 (22.2)	1 (1.0)
Lymphocytosis	1 (11.1)	0
Malaise	1 (11.1)	0
Serious adverse events		
Thrombocytopenia	1 (11.1)	3 (3.1)
Neutropenia	1 (11.1)	1 (1.0)
Fatigue	1 (11.1)	0

Although some adverse events were reported at a ≥10% higher incidence in the Japanese population than in the entire non-Japanese population, the trend of occurrence of adverse events in Japanese patients was largely similar to that in the overall all treated analysis set. There were no major safety issues unique to the Japanese population.

PMDA’sview:

Serious adverse events were reported frequently in Study MMY2001. Following Carvykti infusion, the patient’s condition should be monitored very closely, and if adverse events occur, multidisciplinary measures should be taken to manage adverse events individually. Although there are limitations to rigorous comparison of the safety of Carvykti between Japanese and non-Japanese populations due to limited clinical experience with Carvykti in Japanese patients, adverse events should be managed more carefully in Japanese patients because febrile neutropenia and other adverse events occurred more frequently in Japanese patients than in non-Japanese patients.

7.R.2.2 Specific events in safety profile of Carvykti

In the following sections, PMDA conducted its safety review, focusing on events with a high incidence and serious adverse events, based on the safety results from Study MMY2001.

7.R.2.2.1 CRS and HLH

The applicant's explanation about CRS associated with Carvykti: (1) the incidences of CRS and HLH in the clinical study, (2) the risk factors for the onset and increased severity of CRS, and (3) CRS management algorithm:

(1) Incidences of CRS and HLH in the clinical study

Events coded to MedDRA PT "cytokine release syndrome" were counted as CRS.

In Study MMY2001, CRS was evaluated according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system (*Biol Blood Marrow Transplant.* 2019*;* 25: 625-38) presented in Table 21.

Table 21. CRS consensus grading (ASTCT consensus grading system)

Grade 1	Fever[*1] (Temperature ≥38.0°C)
Grade 2	Fever[*1] (Temperature ≥38.0°C) with hypotension not requiring vasopressors and/or[*2] hypoxia requiring low-flow nasal cannula[*3] or blow-by
Grade 3	Fever[*1] (Temperature ≥38.0°C) with hypotension requiring a vasopressor with or without vasopressin and/or[*2] hypoxia requiring high-flow nasal cannula,[*3] facemask, nonrebreather mask, or Venturi mask
Grade 4	Fever[*1] (Temperature ≥38.0°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and/or[*2] hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
Grade 5	Death

*1 Fever is defined as temperature ≥38.0°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

*2 CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

*3 Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min or blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

Table 22 shows the incidence of CRS-related events in Study MMY2001.

Table 22. Incidence of CRS
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

	n (%)			
	Japanese population	Non-Japanese population		
	N = 9	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
All adverse events	8 (88.9)	27 (93.1)	65 (95.6)	92 (94.8)
Grade ≥3 adverse events	0	3 (10.3)	2 (2.9)	5 (5.2)
Serious adverse events	1 (11.1)	5 (17.2)	15 (22.1)	20 (20.6)
Adverse events leading to death	0	1 (3.7)	0	1 (1.0)
Median time to first onset (Range) (days)	7.5 (4-11)	7.0 (2-12)	7.0 (1-10)	7.0 (1-12)
Median duration of CRS (Range) (days)	5.0 (2-6)	3.0 (2-97)	4.0 (1-14)	4.0 (1-97)

Table 23 shows the details of patients with serious or Grade ≥3 CRS in Study MMY2001. CRS leading to death occurred in 1 subject (a non-Japanese subject, the phase Ib part).[20)] The subject also experienced HLH and died. All subjects with CRS had an outcome of "resolved," except for the 1 fatal case. In Study MMY2001, HLH was reported in this 1 patient only.

Table 23. Listing of patients with serious or Grade ≥3 CRS (Study MMY2001)

Age	Sex	Japanese/ Non-Japanese	Grade	Seriousness	Causality	Time to onset (Days after infusion)	Duration (days)	Outcome	Use/Number of doses of tocilizumab
5[redacted]	M	Japanese	1	Serious	Yes	4	5	Resolved	Yes/4
5[redacted]	M	Non-Japanese	3	Serious	Yes	10	5	Resolved	Yes/1
6[redacted]	M	Non-Japanese	1	Serious	Yes	11	3	Resolved	No
6[redacted]	M	Non-Japanese	1	Serious	Yes	10	4	Resolved	Yes/1
6[redacted]	F	Non-Japanese	4	Serious	Yes	8	2	Resolved	Yes/1
7[redacted]	M	Non-Japanese	3	Serious	Yes	11	2	Resolved	Yes/5
			4	Serious	Yes	13	86	Resolved	
			5	Serious	Yes	99	1	Fatal	
5[redacted]	M	Non-Japanese	1	Serious	Yes	7	4	Resolved	No
6[redacted]	M	Non-Japanese	1	Serious	Yes	10	3	Resolved	Yes/1
6[redacted]	M	Non-Japanese	1	Serious	Yes	5	3	Resolved	Yes/2
5[redacted]	M	Non-Japanese	1	Serious	Yes	7	2	Resolved	Yes/2
5[redacted]	M	Non-Japanese	3	Serious	Yes	13	1	Resolved	Yes/1
4[redacted]	F	Non-Japanese	3	Serious	Yes	8	7	Resolved	Yes/1
5[redacted]	M	Non-Japanese	1	Serious	Yes	9	3	Resolved	No
6[redacted]	M	Non-Japanese	2	Serious	Yes	10	3	Resolved	No
5[redacted]	F	Non-Japanese	2	Serious	Yes	11	3	Resolved	Yes/2
7[redacted]	F	Non-Japanese	1	Serious	Yes	14	6	Resolved	Yes/1
7[redacted]	M	Non-Japanese	2	Serious	Yes	2	7	Resolved	Yes/2
5[redacted]	F	Non-Japanese	1	Serious	Yes	10	4	Resolved	No
7[redacted]	F	Non-Japanese	2	Serious	Yes	10	2	Resolved	Yes/2
6[redacted]	F	Non-Japanese	1	Serious	Yes	7	6	Resolved	Yes/3
6[redacted]	M	Non-Japanese	1	Serious	Yes	9	3	Resolved	No

(2) Risk factors for the onset and increased severity of CRS

Data suggest that cytokines released following CAR-T cell recognition of target cells play an important role in the development of CRS. High tumor burden prior to administration of a CAR-T cell product (*Oncology*. 2019; 37: 48-52, *Blood*. 2016; 127: 3321-30), active infection (*Cancers*. 2021; 13: 1684, *Br J Haematol*. 2018; 183: 364-74), early onset of fever after administration of a CAR-T cell product (*Br J Haematol*. 2018; 183: 364-74, *Blood*. 2017; 130: 2295-306), and persistent fever after administration of a CAR-T cell product (*Blood*. 2017; 130: 2295-306, *Sci Transl Med*. 2014; 6: 224ra25) have been reported to be associated with severe CRS.

In Study MMY2001, inflammatory cytokines were elevated with the onset of CRS. One subject had CRS associated with secondary HLH, with a fatal outcome.

The results of analyses for the reported factors for severe CRS in Study MMY2001 (the non-Japanese population) are shown below.

- The incidences of Grade ≥3 CRS by baseline tumor burden[25)] were 12.5% (2 of 16 subjects) for high tumor burden, 4.5% (1 of 22 subjects) for intermediate tumor burden, and 3.4% (2 of 59 subjects) for low tumor burden.

[25)] High tumor burden was defined as any one of the following: bone marrow plasma cells ≥80%; serum M-spike ≥5 g/dL; serum FLC ≥5000 mg/L. Subjects who did not meet the criteria for either high or low tumor burden were classified as having intermediate tumor burden.
Low tumor burden was defined as all of the following: bone marrow plasma cells <50%; serum M-spike <3 g/dL; serum FLC <3000 mg/L.

- The incidences of Grade ≥3 CRS in patients with or without active infection between LD chemotherapy and CRS resolution were 20.0% (2 of 10 subjects) and 3.4% (3 of 87 subjects), respectively.
- Fever as a CRS-associated symptom was reported in all patients with CRS. The median time to the onset of fever and the median duration of fever (range) were 7.0 days (1-12 days) and 4.0 days (1-14 days), respectively, in patients with Grade 1 or 2 CRS, and 6.0 days (3-9 days) and 5.0 days (3-11 days), respectively, in patients with Grade ≥3 CRS.

As described in the above, the results of Study MMY2001 were largely consistent with the previously reported information. However, the number of patients with Grade ≥3 CRS is limited, and the pathogenesis of and risk factors for CRS observed after Carvykti infusion have not fully been elucidated. Thus, the applicant will continuously collect the information on the development of CRS as post-marketing pharmacovigilance activities and provide it as needed.

(3) CRS management algorithm

Table 24 shows CRS management algorithm employed in Study MMY2001.

Table 24. CRS management algorithm (Study MMY2001)

Grade	Presenting symptoms	Tocilizumab	Corticosteroids
Grade 1	Temperature ≥38℃	May be considered	Not applicable
Grade 2	Temperature ≥38℃ with either: ● Hypotension responsive to fluids and not requiring vasopressors. OR ● Condition requiring oxygen via low-flow nasal cannula* or blow-by	● Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg/body). ● Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. ● Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses, if no clinical improvement in the signs and symptoms of CRS	Manage per guidance below if no improvement within 24 hours of starting tocilizumab. ● Administer methylprednisolone 1 mg/kg intravenously twice daily or dexamethasone 10 mg intravenously every 6 hours. ● Continue corticosteroids until the severity of the event is Grade 1 or less, then taper over 3 days.
Grade 3	Temperature ≥38℃ with either: ● Hypotension requiring one vasopressor with or without vasopressin. OR ● Condition requiring oxygen via high-flow nasal cannula,* facemask, non-rebreather mask, or Venturi mask	● Per Grade 2	● Per Grade 2
Grade 4	Temperature ≥38℃ with either: ● Hypotension requiring multiple vasopressors (excluding vasopressin) OR ● Condition requiring oxygen under positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)	● Per Grade 2	● Manage as Grade 2 above or administer methylprednisolone 1,000 mg intravenously once daily for 3 days upon the discretion of the physician. ● If no improvement or if condition worsens, consider alternate immunosuppressants (e.g., monoclonal antibodies targeting cytokines).

* Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

PMDA's view:

In the clinical study, CRS occurred frequently after Carvykti infusion, and serious CRS and fatal CRS associated with HLH were also reported. As shown in Table 22, CRS occurred 1 to 2 days after Carvykti infusion in some patients. Given these findings, Carvykti should be administered in an inpatient setting, and close monitoring is needed especially during the early phase after Carvykti infusion. The applicant should appropriately provide precautionary information, including the incidences of CRS and HLH and the methods of managing CRS in the clinical study, to healthcare professionals in clinical practice, using the package insert and other materials. Furthermore, precautionary information should be provided appropriately using the package insert and other materials to ensure that Carvykti is used by physicians with adequate knowledge of and experience in general care of critical conditions such as CRS and hematological malignancies at a medical institution with an intensive care unit (ICU) etc. that can promptly provide general care in case of emergencies.

7.R.2.2.2 Neurologic disorder

The applicant categorized neurologic disorder associated with Carvykti into 2 types: (1) CAR-T cell-related neurotoxicity (ICANS and other neurotoxicities) and (2) nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity, and explained these events as follows:

(1) CAR-T cell-related neurotoxicity (ICANS and other neurotoxicities)

Tables 25 and 26 show the incidence of CAR-T cell-related neurotoxicity (ICANS and other neurotoxicities) reported as neurologic disorder-related events in Study MMY2001.

Table 25. Incidence of CAR-T cell-related neurotoxicity (Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

	n (%)			
	Japanese population	Non-Japanese population		
	N = 9	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
Any CAR-T cell-related neurotoxicity				
All adverse events	0	4 (13.8)	16 (23.5)	20 (20.6)
Grade ≥3 adverse events	0	1 (3.4)	9 (13.2)	10 (10.3)
Serious adverse events	0	2 (6.9)	13 (19.1)	15 (15.5)
Adverse events leading to death	0	0	1 (1.5)	1 (1.0)
Median time to first onset (Range) (days)	—	8.0 (3-26)	8.0 (4-101)	8.0 (3-101)
Median duration (Range) (days)	—	4.5 (2-70)	51.0 (2-519)	34.0 (2-519)
ICANS				
All adverse events	0	3 (10.3)	13 (19.1)	16 (16.5)
Grade ≥3 adverse events	0	1 (3.4)	1 (1.5)	2 (2.1)
Serious adverse events	0	1 (3.4)	4 (5.9)	5 (5.2)
Adverse events leading to death	0	0	0	0
Median time to first onset (Range) (days)	—	8.0 (3-8)	8.0 (4-12)	8.0 (3-12)
Median duration (Range) (days)	—	3.0 (2-6)	4.0 (1-12)	4.0 (1-12)
Other neurotoxicities				
All adverse events	0	1 (3.4)	11 (16.2)	12 (12.4)
Grade ≥3 adverse events	0	0	9 (13.2)	9 (9.3)
Serious adverse events	0	1 (3.4)	10 (14.7)	11 (11.3)
Adverse events leading to death	0	0	1 (1.5)	1 (1.0)
Median time to first onset (Range) (days)	—	26.0	27.0 (11-108)	26.5 (11-108)
Median duration (Range) (days)	—	70.0	79.0 (2-482)	74.5 (2-482)

Table 26. CAR-T cell-related neurotoxicity events reported by ≥3% of subjects in the entire non-Japanese population (Study MMY2001, All treated analysis set, data cutoff date of February 11, 2021)

PT (MedDRA/J Version23.0)	n (%)					
	Non-Japanese population					
	Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any CAR-T cell-related neurotoxicity	4 (13.8)	1 (3.4)	16 (23.5)	9 (13.2)	20 (20.6)	10 (10.3)
ICANS	3 (10.3)	1 (3.4)	13 (19.1)	1 (1.5)	16 (16.5)	2 (2.1)
Aphasia	0	0	5 (7.4)	0	5 (5.2)	0
Confusional state	1 (3.4)	0	4 (5.9)	1 (1.5)	5 (5.2)	1 (1.0)
Micrographia	0	0	4 (5.9)	0	4 (4.1)	0
Parkinsonism	0	0	4 (5.9)	3 (4.4)	4 (4.1)	3 (3.1)
Mental status changes	0	0	4 (5.9)	3 (4.4)	4 (4.1)	3 (3.1)
Gait disturbance	1 (3.4)	0	3 (4.4)	0	4 (4.1)	0
Disturbance in attention	1 (3.4)	0	2 (2.9)	0	3 (3.1)	0
Dysgraphia	0	0	3 (4.4)	1 (1.5)	3 (3.1)	1 (1.0)
Memory impairment	1 (3.4)	0	2 (2.9)	0	3 (3.1)	0
Reduced facial expression	0	0	3 (4.4)	0	3 (3.1)	0
Somnolence	0	0	3 (4.4)	1 (1.5)	3 (3.1)	1 (1.0)
Tremor	0	0	3 (4.4)	0	3 (3.1)	0

Neurologic disorder leading to death occurred in 1 subject in the non-Japanese population (neurotoxicity), and its causal relationship to Carvykti could not be ruled out.

Table 27 shows the details of patients with serious or Grade ≥3 CAR-T cell-related neurotoxicity in Study MMY2001.

Table 27. Listing of patients with serious or Grade ≥3 CAR-T cell-related neurotoxicity (Study MMY2001)

Age	Sex	PT (MedDRA/J ver.23.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causality to Carvykti	Outcome
6[redacted]	M	ICANS	2	Serious	13	3	Yes	Resolved
		ICANS	1	Serious	15	3	Yes	Resolved
6[redacted]	F	Depressed level of consciousness	3	Serious	8	2	Yes	Resolved
		ICANS	3	Serious	8	2	Yes	Resolved
6[redacted]	F	Facial paralysis	2	Serious	26	70	Yes	Resolved
5[redacted]	M	Parkinsonism	1	Serious	101	5	Yes	Not resolved
		Parkinsonism	2	Serious	105	—	Yes	Not resolved
6[redacted]	F	Neurotoxicity	4	Serious	93	—	Yes	Not resolved
5[redacted]	M	Mental status changes	3	Serious	100	148	Yes	Not resolved
		Parkinsonism	3	Non-serious	105	—	Yes	Not resolved
		Neurotoxicity	5	Serious	247	1	Yes	Fatal
6[redacted]	M	ICANS	2	Serious	5	4	Yes	Resolved
7[redacted]	M	Diplopia	3	Serious	11	2	Yes	Resolved
6[redacted]	M	Muscular weakness	3	Serious	108	10	Yes	Resolving
		Personality change	3	Non-serious	108	5	Yes	Resolved
		Mental status changes	3	Serious	110	8	Yes	Resolving
		Asthenia	3	Serious	130	223	Yes	Resolving
		Confusional state	3	Serious	130	23	Yes	Resolved
		Dysgraphia	3	Non-serious	130	259	Yes	Resolved
		Motor dysfunction	3	Non-serious	130	286	Yes	Resolved
		Personality change	3	Non-serious	132	17	Yes	Resolved
		Peripheral motor neuropathy	3	Non-serious	136	217	Yes	Resolving
		Peroneal nerve palsy	3	Non-serious	136	217	Yes	Resolving
		Personality change	3	Non-serious	168	4	Yes	Resolved
		Stereotypy	3	Non-serious	168	2	Yes	Resolved
6[redacted]	M	ICANS	1	Serious	10	4	Yes	Resolved
7[redacted]	F	Peripheral motor neuropathy	3	Serious	74	54	Yes	Resolved
		Peripheral sensory neuropathy	3	Serious	74	9	Yes	Resolved
7[redacted]	M	Parkinsonism	3	Serious	29	28	Yes	Resolving
		Parkinsonism	1	Serious	56	—	Yes	Not resolved
7[redacted]	M	Cranial nerve paralysis	3	Serious	21	6	Yes	Not resolved
		Cranial nerve paralysis	3	Non-serious	26	54	Yes	Resolving
7[redacted]	M	ICANS	3	Serious	6	1	Yes	Resolved
		ICANS	4	Serious	7	3	Yes	Resolved
		ICANS	3	Serious	10	5	Yes	Resolved
		Mental status changes	3	Serious	17	—	Yes	Not resolved
6[redacted]	M	Parkinsonism	3	Serious	30	—	Yes	Not resolved
		Somnolence	3	Serious	64	5	Yes	Resolved

For CAR-T cell-related neurotoxicity (ICANS and other neurotoxicities), the following findings have been obtained to date:

- CRS has been reported as a risk factor for ICANS. Multiple studies have revealed that in many cases, ICANS occurs after the onset of CRS, and that severe ICANS develops in the presence of severe CRS (*Front Immunol*. 2020; 11: 577027).
- A patient who received treatment with a CAR-T cell product died from progressive neurologic deterioration. Autopsy findings included diffuse gliosis with severe, widespread neuronal loss and degeneration of white matter and macrophage infiltration with numerous microglial cells and CD8+ T-cell infiltrate (*J Natl Cancer Inst*. 2019; 111: 646-54).

As with the above reports, in Study MMY2001, all patients with ICANS had CRS. Brain autopsies in 2 patients with neurologic disorder revealed gliosis.

Neurologic disorder with altered motor and neurocognitive functions that are not defined as ICANS[26)] (hereinafter referred to as "movement and neurocognitive adverse events") occurred in 5 subjects in the phase II part of Study MMY2001, and some of them had severe events or had not recovered at the time of death. Of these 5 subjects, 1 had Grade 2 event, and 4 had Grade 3 events. The events reported by ≥2 subjects were parkinsonism (4 subjects), micrographia (4 subjects), reduced facial expression (3 subjects), bradykinesia (2 subjects), memory impairment (2 subjects), gait disturbance (2 subjects), tremor (2 subjects), and mental status changes (2 subjects). Grade ≥3 events were parkinsonism (3 subjects), mental status changes (2 subjects), personality change (1 subjects), confusional state (1 subjects), dysgraphia (1 subjects), motor dysfunction (1 subjects), and stereotypy (1 subjects) (some subjects had more than 1 event).[27)] The median time to onset from Carvykti infusion (range) was 27.0 days (14-108 days).

As of the data cutoff date of February 11, 2021, three subjects died. The causes of deaths were neurotoxicity, septic shock, and lung abscess. Two of the 3 subjects were autopsied. Although the autopsy findings from the 1 patient showed focal gliosis and T-cell infiltrates (CD8+ > CD4+) in the basal ganglia, it is unknown if these were CAR-T cells. No abnormalities were reported in other brain regions potentially associated with movement disorder (e.g., cerebellum, substantia nigra), and there was preservation of pigmentation in the substantia nigra. In the other 2 subjects, some events resolved or improved, but others were persistent.

Between the data cutoff date of February 11, 2021 and [redacted], 20[redacted], movement and neurocognitive adverse events were newly reported in 1 subject in the non-Japanese population (the phase Ib part) of Study MMY2001. The patient experienced cognitive disorder and gait disturbance (both Grade 1) and tremor (Grade 3) on Day 914, with a duration of 83 days. Anti-cytokine therapy such as corticosteroids was not initiated, and all events improved except for gait disturbance with an outcome of "not resolved."

In ongoing Study MMY2003[28)] and Study MMY3002,[29)] 1 subject in Study MMY2003 experienced movement and neurocognitive adverse events (bradykinesia, bradyphrenia, cognitive disorder, encephalopathy, gait

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26) Movement disorder-related events: MedDRA PTs "ataxia," "balance disorder," "bradykinesia," "cogwheel rigidity," "dysgraphia," "dyskinesia," "dysmetria," "essential tremor," "gait disturbance," "hand-eye coordination impaired," "micrographia," "motor dysfunction," "myoclonus," "parkinsonism," "posture abnormal," "resting tremor," "stereotypy," "tremor"
Cognitive disorder-related events: MedDRA PTs "amnesia," "apraxia," "bradyphrenia," "cognitive disorder," "confusional state," "depressed level of consciousness," "disturbance in attention," "encephalopathy," "incoherent," "leukoencephalopathy," "loss of consciousness," "memory impairment," "mental impairment," "mental status changes," "noninfective encephalitis," "psychomotor retardation"
Personality change-related events: MedDRA PTs "flat affect," "personality change," "reduced facial expression"

27) Symptomatic therapies used included corticosteroids, cyclophosphamide, intrathecal chemotherapy (methotrexate, cytarabine), IL-1 receptor antagonist (anakinra), tyrosine kinase inhibitor (dasatinib), anti-IL-6 antibody (siltuximab), and other drugs (e.g., carbidopa/levodopa, levetiracetam).

28) A multi-cohort, open-label, multicenter phase II study to evaluate the minimal residual disease (MRD) negative rate of adult patients with MM treated with Carvykti. The study is ongoing in the US, Europe, and other countries.

29) An open-label, randomized, global phase III study to evaluate the efficacy and other aspects of Carvykti versus chemotherapy chosen by the investigator [pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd)] in patients with relapsed or lenalidomide-refractory MM who have received 1 to 3 prior lines of therapy.

disturbance, and motor dysfunction; all Grade 3) as of [redacted], 20[redacted]. The events occurred 38 days after Carvykti infusion with a duration of 89 days. The events were treated with corticosteroids, plasmapheresis, etc., with an outcome of "not resolved."

The risk factors for movement and neurocognitive adverse events were identified as follows:
In Study MMY2001 (data cutoff date of February 11, 2021), the proportion of subjects by baseline tumor burden[25)] among the 5 subjects with movement and neurocognitive adverse events was 60.0% (3 subjects) for high tumor burden and 20.0% each (1 subject) for intermediate and low tumor burden. The 1 subject with low tumor burden had extramedullary plasmacytoma (the sum of the products of the greatest diameters, 2,348 mm^2). All 5 subjects received bridging therapy. Three subjects (60.0% of the subjects) experienced an increase in tumor burden from baseline to Carvykti infusion, 1 subject (20.0% of the subjects) did not experience an increase in tumor burden, and 1 subject (20.0% of the subjects) was not evaluable. On the other hand, among 92 subjects without movement and neurocognitive adverse events, the proportion of subjects by baseline tumor burden was 14.1% (13 subjects) for high tumor burden, 22.8% (21 subjects) for intermediate tumor burden, and 63.0% (58 subjects) for low tumor burden.

All of the 5 subjects with movement and neurocognitive adverse events had Grade ≥2 CRS after Carvykti infusion, and 4 had Grade 1 ICANS. Both CRS and ICANS resolved before the onset of movement and neurocognitive adverse events.

The blood CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in patients with or without movement and neurocognitive adverse events were compared. CAR transgene levels were higher in patients with than in those without movement and neurocognitive adverse events [see Section 6.1.1], and the time to reach peak levels of blood CAR transgene tended to be increased in the 5 subjects with movement and neurocognitive adverse events.

The 1 subject with movement and neurocognitive adverse events in Study MMY2003 also had high tumor burden at baseline and experienced Grade 4 CRS after Carvykti infusion, but did not have ICANS. The 1 non-Japanese patient with movement and neurocognitive adverse events newly reported by [redacted], 20[redacted] in Study MMY2001 had low tumor burden at baseline, but experienced Grade 2 CRS and Grade 3 ICANS after Carvykti infusion.

As described in the above, movement and neurocognitive adverse events occur after the recovery from CRS or ICANS, and are characterized by the symptoms of parkinsonism. The risk of movement and neurocognitive adverse events was associated with a combination of 2 or more factors such as (i) high tumor burden, (ii) prior Grade ≥2 CRS or prior ICANS of any grade, and (iii) high CAR-T cell expansion or persistence. These events were non-responsive to steroids, and tended to have longer duration than ICANS. Enhanced bridging

chemotherapy to reduce baseline tumor burden and aggressive treatment of CRS and ICANS are considered important for toxicity management (*Blood Cancer J*. 2022; 12: 32).

Based on the information on these risk factors, the protocols for the ongoing clinical studies including Study MMY2001 were amended to implement the following safety measures and additional monitoring.

(a) Reduce tumor burden with bridging therapy in patients with high tumor burden at screening.
(b) Early and aggressive supportive care (including steroids) for CRS (Grade ≥2) or ICANS (any Grade)
(c) Implement safety measures, e.g., consideration of CAR-T ablation in the event of no improvement in neurologic symptoms.
(d) Early detection and treatment are considered important for the prevention of worsening of neurotoxicity. For this reason, qualitative changes from baseline in handwriting assessment should be monitored as an early clinical predictive marker. If neurologic or psychiatric symptoms are observed, tests such as diagnostic imaging, serological or cerebrospinal fluid examinations are recommended.

After the implementation of the above additional monitoring and safety measures, ≥250 patients received Carvykti in the clinical studies. The incidence of movement and neurocognitive adverse events was reduced from 5% to <0.5% by the implementation of the additional monitoring and safety measures.

The applicant will provide precautionary information, including monitoring and safety measures as well as the risk factors, using information materials etc. in the post-marketing setting. Since the pathogenesis of neurologic disorder observed after Carvykti infusion and its risk factors are still unknown, the applicant will collect information on the occurrence of neurologic disorder continuously as post-marketing pharmacovigilance activities and provide it to healthcare professionals, as needed.

(2) Nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity

Tables 28 and 29 show the incidence of nervous system disorders (events that are coded to the MedDRA SOC "nervous system disorders" or "psychiatric disorders" and that are not categorized as CAR-T cell-related neurotoxicity) in Study MMY2001.

Table 28. Incidence of nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity (Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

	n (%)			
	Japanese population	Non-Japanese population		
	N = 9	Phase Ib N = 29	Phase II N = 68	Phase Ib + Phase II N = 97
All adverse events	4 (44.4)	21 (72.4)	41 (60.3)	62 (63.9)
Grade ≥3 adverse events	0	1 (3.4)	2 (2.9)	3 (3.1)
Serious adverse events	0	2 (6.9)	2 (2.9)	4 (4.1)
Adverse events leading to death	0	0	0	0
Median time to first onset (Range) (days)	20.5 (8-77)	8.0 (1-79)	8.0 (1-99)	8.0 (1-99)
Median duration (Range) (days)	4.5 (1-7)	66.0 (1-927)	56.0 (1-578)	60.5 (1-927)

Table 29. Nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity and that occurred in ≥3% of subjects in the entire non-Japanese population or Japanese population (Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

PT (MedDRA/J ver.23.0)	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any nervous system disorder	4 (44.4)	0	21 (72.4)	1 (3.4)	41 (60.3)	2 (2.9)	62 (63.9)	3 (3.1)
Headache	3 (33.3)	0	10 (34.5)	0	15 (22.1)	0	25 (25.8)	0
Dizziness	0	0	5 (17.2)	0	15 (22.1)	0	20 (20.6)	0
Insomnia	0	0	2 (6.9)	0	11 (16.2)	0	13 (13.4)	0
Confusional state	0	0	1 (3.4)	0	5 (7.4)	0	6 (6.2)	0
Anosmia	0	0	0	0	5 (7.4)	0	5 (5.2)	0
Dysgeusia	0	0	1 (3.4)	0	4 (5.9)	0	5 (5.2)	0
Peripheral sensory neuropathy	0	0	2 (6.9)	0	2 (2.9)	0	4 (4.1)	0
Paraesthesia	0	0	1 (3.4)	0	2 (2.9)	0	3 (3.1)	0
Tremor	0	0	1 (3.4)	0	2 (2.9)	0	3 (3.1)	0
Anxiety	0	0	2 (6.9)	0	1 (1.5)	0	3 (3.1)	0
Depression	0	0	1 (3.4)	0	2 (2.9)	0	3 (3.1)	0
Somnolence	1 (11.1)	0	2 (6.9)	0	0	0	2 (2.1)	0

Table 30 shows the details of patients with serious or Grade ≥3 nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity in Study MMY2001.

Table 30. Listing of patients with serious or Grade ≥3 nervous system disorders that are not categorized as CAR-T cell-related neurotoxicity

Age	Sex	PT (MedDRA/J ver.23.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causality to Carvykti	Outcome
6[redacted]	M	Confusional state	1	Serious	13	2	No	Resolved
5[redacted]	M	Noninfective encephalitis	3	Serious	26	3	Yes	Resolved
6[redacted]	M	Syncope	3	Serious	40	1	No	Resolved
6[redacted]	F	Neuralgia	3	Serious	49	2	No	Resolved

PMDA's view:

In the clinical study, CAR-T cell-related neurotoxicity and other neurologic disorders occurred frequently after Carvykti infusion, and such events included serious and Grade ≥3 events. Movement and neurocognitive adverse events, which are non-responsive to steroids and mainly characterized by parkinsonism, were reported. There were patients with Grade ≥3 or serious parkinsonism who died. The patient's condition should be closely monitored for signs and symptoms of these neurologic disorders following Carvykti infusion. The applicant should appropriately provide precautionary information, including the incidence of neurologic disorder, a breakdown of the reported events, and management strategies in the clinical study, to healthcare professionals in clinical practice, using the package insert and other materials.

7.R.2.2.3 Infections

The applicant's explanation about infections associated with the use of Carvykti:

Tables 31 and 32 show events coded to the MedDRA SOC "infections and infestations" that were counted as infections. In Study MMY2001, the protocol specified that prophylactic, pre-emptive, or therapeutic antibacterials, antifungals, anti-neumocystis agents, and antivirals were to be considered according to the institutional guidelines.[30)]

Table 31. Incidence of infections
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

High level group term (MedDRA/J ver.23.0)	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any infection	1 (11.1)	0	18 (62.1)	4 (13.8)	38 (55.9)	18 (26.5)	56 (57.7)	22 (22.7)
Bacterial infectious disorders	0	0	2 (6.9)	0	6 (8.8)	1 (1.5)	8 (8.2)	1 (1.0)
Viral infectious disorders	0	0	5 (17.2)	1 (3.4)	17 (25.0)	6 (8.8)	22 (22.7)	7 (7.2)
Fungal infectious disorders	0	0	0	0	1 (1.5)	1 (1.5)	1 (1.0)	1 (1.0)
Protozoal infectious disorders	0	0	1 (3.4)	1 (3.4)	0	0	1 (1.0)	1 (1.0)
Infections - pathogen unspecified	1 (11.1)	0	16 (55.2)	4 (13.8)	23 (33.8)	13 (19.1)	39 (40.2)	17 (17.5)

Table 32. Infections reported by ≥5% of subjects in the entire non-Japanese population or Japanese population
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

PT (MedDRA/J ver.23.0)	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any infection	1 (11.1)	0	18 (62.1)	4 (13.8)	38 (55.9)	18 (26.5)	56 (57.7)	22 (22.7)
Upper respiratory tract infection	1 (11.1)	0	9 (31.0)	0	6 (8.8)	1 (1.5)	15 (15.5)	1 (1.0)
Pneumonia	0	0	3 (10.3)	3 (10.3)	6 (8.8)	6 (8.8)	9 (9.3)	9 (9.3)
Rhinovirus infection	0	0	2 (6.9)	0	4 (5.9)	2 (2.9)	6 (6.2)	2 (2.1)
Influenza	0	0	1 (3.4)	0	4 (5.9)	2 (2.9)	5 (5.2)	2 (2.1)
Sepsis	0	0	1 (3.4)	1 (3.4)	4 (5.9)	4 (5.9)	5 (5.2)	5 (5.2)
Bacteraemia	1 (11.1)	0	0	0	1 (1.5)	0	1 (1.0)	0

Infections leading to death occurred in 3 subjects in the phase II part (lung abscess, sepsis, and septic shock [1 subject each]).

Serious infections occurred in 21 subjects (4 in the phase Ib part, 17 in the phase II part). No serious infections were reported in the Japanese population. Serious infections reported by ≥2 subjects in the entire non-Japanese population were pneumonia (5 subjects), sepsis (5 subjects), and rhinovirus infection (2 subjects).

PMDA's view:

Since infections leading to death, Grade ≥3 infections, and serious infections were reported following administration of Carvykti, patients should be monitored for signs and symptoms of infections following

[30)] Prophylactic antibacterials, antifungals, and antivirals were administered in 72.2%, 68.0%, and 99.0%, respectively, of subjects in the non-Japanese population of Study MMY2001.

Carvykti infusion. The applicant should appropriately provide precautionary information, including the incidence of infections etc. in the clinical study, to healthcare professionals in clinical practice, using the package insert and other materials.

7.R.2.2.4 Cytopenias

The applicant's explanation about cytopenias associated with Carvykti:

Table 33 shows cytopenic adverse events (including febrile neutropenia) coded to the MedDRA SOC "blood and lymphatic system disorders" that were counted as cytopenia-related events.

Table 33. Incidence of cytopenias
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

SOC PT (MedDRA/J ver.23.0)	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood and lymphatic system disorders	8 (88.9)	8 (88.9)	29 (100)	29 (100)	68 (100)	67 (98.5)	97 (100)	96 (99.0)
Neutropenia	8 (88.9)	8 (88.9)	29 (100)	29 (100)	64 (94.1)	63 (92.6)	93 (95.9)	92 (94.8)
Febrile neutropenia	3 (33.3)	3 (33.3)	1 (3.4)	1 (3.4)	9 (13.2)	8 (11.8)	10 (10.3)	9 (9.3)
Anaemia	6 (66.7)	6 (66.7)	22 (75.9)	15 (51.7)	57 (83.8)	51 (75.0)	79 (81.4)	66 (68.0)
Thrombocytopenia	7 (77.8)	7 (77.8)	25 (86.2)	20 (69.0)	52 (76.5)	38 (55.9)	77 (79.4)	58 (59.8)
Leukopenia	4 (44.4)	4 (44.4)	20 (69.0)	20 (69.0)	40 (58.8)	39 (57.4)	60 (61.9)	59 (60.8)
Lymphopenia	0	0	16 (55.2)	15 (51.7)	35 (51.5)	33 (48.5)	51 (52.6)	48 (49.5)

Table 34 shows the time to the first onset and duration of cytopenia.

Table 34. Time to first onset and duration of cytopenia
(Study MMY2001, All treated analysis set, data cutoff date of July 22, 2021 for Japanese population, data cutoff date of February 11, 2021 for non-Japanese population)

PT (MedDRA/J ver.23.0)	Median (days) Range (days)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
	Time to onset*	Duration	Time to onset*	Duration	Time to onset*	Duration	Time to onset*	Duration
Anaemia	3.0 1-10	85.0 19-521	2.5 −1 to 44	37.5 2-661	4.0 −1 to 125	43.0 1-580	4.0 −1 to 125	42.0 1-661
Neutropenia	3.0 −5 to 22	73.5 39-363	1.0 1-9	65.0 15-156	2.0 −1 to 30	56.0 2-548	2.0 −1 to 30	57.0 2-548
Leukopenia	0 −3 to 2	70.0 26-104	1.0 −1 to 7	63.0 9-675	1.0 −4 to 32	53.5 2-571	1.0 −4 to 32	59.0 2-675
Febrile neutropenia	6.0 2-10	7.0 5-8	58.0	5	8.0 1-51	5.0 1-29	8.0 1-58	5.0 1-29
Lymphopenia	—	—	8.0 −1 to 29	23.5 2-923	1.0 −4 to 33	166.0 2-612	5.0 −4 to 33	60.0 2-923
Thrombocytopenia	10.0 2-26	32.0 15-353	10.0 1-24	85.0 2-600	5.5 −10 to 101	100.5 1-529	8.0 −10 to 101	93.0 1-600

*: Days after Carvykti infusion

No cytopenias leading to death were reported. Serious cytopenias occurred in 7 of 97 subjects (7.2%) in the non-Japanese population, including febrile neutropenia (4 subjects [1 in the phase Ib part, 3 in the phase II part]), thrombocytopenia (3 subjects [1 in the phase Ib part, 2 in the phase II part]), and neutropenia (1 subject

in the phase II part). Serious neutropenia and thrombocytopenia occurred in 1 of 9 subjects (11.1%) in the Japanese population.

PMDA's view:
Since serious cytopenias were reported in the clinical study, patients should be monitored for signs and symptoms of cytopenias following administration of Carvykti. The applicant should appropriately provide information, including the incidence and time to onset of cytopenias in the clinical study, to healthcare professionals in clinical practice, using the package insert and other materials. In addition, the applicant should appropriately provide precautionary information to healthcare professionals in clinical practice, using the package insert and other materials, to ensure that blood tests are performed regularly after Carvykti infusion and that cytopenia is managed appropriately if it occurs.

7.R.2.2.5 Hypersensitivity

The applicant's explanation about hypersensitivity associated with Carvykti:
Events coded to the MedDRA SMQ (narrow) "hypersensitivity" occurring within 24 hours of Carvykti infusion were counted as hypersensitivity. In Study MMY2001, hypersensitivity occurred in 5 subjects (5.2%) in the non-Japanese population only (data cutoff date of February 11, 2021), including flushing (4 subjects [4.1%]); chest discomfort (2 subjects [2.1%]); and burning sensation, tremor, tachycardia, and wheezing (1 subject each [1.0%]). No serious or Grade ≥3 events were reported. No hypersensitivity was reported in the Japanese population (data cutoff date of July 22, 2021). The protocol of the clinical study of Carvykti specified that subjects were to be premedicated with acetaminophen 650 to 1,000 mg and diphenhydramine 50 mg.

PMDA's view:
Although no Grade ≥3 or serious hypersensitivity has been reported in the clinical study so far, Grade ≥3 hypersensitivity and serious hypersensitivity have been reported with the approved anti-CD19 or anti-BCMA CAR-T cell products. Hypersensitivity is an event that requires attention. Given these points, patients should be monitored for signs and symptoms of hypersensitivity following treatment with Carvykti as well. Thus, the applicant should appropriately provide precautionary information, including the incidence of hypersensitivity and the premedications specified in the clinical study, to healthcare professionals in clinical practice, using the package insert and other materials.

7.R.2.2.6 Hypogammaglobulinaemia

The applicant's explanation about hypogammaglobulinaemia associated with Carvykti:
MedDRA PT "hypogammaglobulinaemia" was counted as hypogammaglobulinaemia-related events.

Hypogammaglobulinaemia occurred in 12 of 97 subjects (12.4%) in the entire non-Japanese population (data cutoff date of February 11, 2021) and 1 of 9 subjects (11.1%) in the Japanese population (data cutoff date of July 22, 2021). Grade ≥3 hypogammaglobulinaemia occurred in 2 of 97 subjects (2.1%) in the non-Japanese

population only. No hypogammaglobulinaemia leading to death or serious hypogammaglobulinaemia was reported.

PMDA's view:
Grade ≥3 hypogammaglobulinaemia was reported after Carvykti infusion in the clinical study, and this is an event that requires attention following administration of the approved anti-CD19 or anti-BCMA CAR-T cell products. Anti-BCMA CAR T-cell therapy may cause B-cell depletion. Given these and other findings, patients should be monitored for signs and symptoms of hypogammaglobulinaemia following administration of Carvykti. The applicant should provide information on the incidence of hypogammaglobulinaemia in the clinical study to healthcare professionals. The applicant should also provide precautionary information appropriately to healthcare professionals in clinical practice, using the package insert and other materials, to ensure that hypogammaglobulinaemia is managed appropriately if it occurs.

7.R.2.2.7 TLS

The applicant's explanation about TLS associated with Carvykti:
MedDRA PT "tumor lysis syndrome" was counted as TLS. In Study MMY2001, TLS (Grade 4) occurred after Carvykti infusion in 1 subject in the non-Japanese population (the phase II part, data cutoff date of February 11, 2021) who had concurrent Grade 3 blood creatinine increased. Both events were considered related to Carvykti. The times from Carvykti infusion to the onset of TLS and blood creatinine increased were 3 days and 11 days, respectively, with durations of 6 days and 7 days, respectively. The events were treated with plasmapheresis and hemodialysis, with outcomes of "resolved" and "resolving," respectively. TLS was not reported in the Japanese population (data cutoff date of July 22, 2021).

In ongoing Studies MMY2003 and MMY3002, no events leading to death or serious events have been reported so far (data cutoff date of [redacted], 20[redacted]).

PMDA's view:
One subject experienced serious Grade 4 TLS for which a causal relationship to Carvykti could not be ruled out in the clinical study. This is an event that requires attention following administration of the approved anti-CD19 or anti-BCMA CAR-T cell products. Given these findings, patients should be monitored for signs and symptoms of TLS following Carvykti infusion. Thus, the applicant should provide information on the incidence of TLS in the clinical study to healthcare professionals. The applicant should also provide the precautionary information appropriately to healthcare professionals in clinical practice, using the package insert and other materials, to ensure that TLS is managed appropriately if it occurs.

7.R.2.2.8 Others

7.R.2.2.8.1 Secondary malignancies

The applicant's explanation about secondary malignancies:

Secondary malignancies occurred in 10 of 97 subjects (10.3%) in the non-Japanese population of Study MMY2001 (data cutoff date of February 11, 2021). The reported events are shown in Table 35. No secondary malignancies were reported in the Japanese population (data cutoff date of July 22, 2021). In clinical studies of Carvykti other than Study MMY2001 (Studies MMY2003 and MMY3002, data cutoff date of [redacted], 20[redacted] for both studies), secondary malignancy of T cell origin has not been reported so far.

Table 35. Listing of patients with secondary malignancies (Study MMY2001)

Age	Sex	PT (MedDRA/J ver.23.0)	Grade	Seriousness	Time to onset (days)	Causality to Carvykti	Outcome
6[redacted]	M	Prostate cancer	3	Serious	141	No	Not resolved
		Acute myeloid leukaemia	3	Serious	338	No	Not resolved
		Acute myeloid leukaemia	5	Serious	418	No	Fatal
5[redacted]	M	Myelodysplastic syndrome	4	Serious	447	No	Not resolved
		Acute myeloid leukaemia	4	Serious	569	No	Not resolved
		Acute myeloid leukaemia	5	Serious	582	No	Fatal
5[redacted]	M	Myelodysplastic syndrome	4	Serious	723	No	Not resolved
6[redacted]	M	Myelodysplastic syndrome	4	Serious	491	No	Not resolved
6[redacted]	F	Myelodysplastic syndrome	4	Serious	478	No	Not resolved
5[redacted]	M	Myelodysplastic syndrome	3	Serious	428	No	Not resolved
7[redacted]	M	Myelodysplastic syndrome	4	Serious	162	No	Not resolved
6[redacted]	M	Basal cell carcinoma	2	Non-serious	47	No	Resolved
5[redacted]	F	Acute myeloid leukaemia	4	Serious	712	No	Not resolved
		Acute myeloid leukaemia	5	Serious	718	No	Fatal
7[redacted]	M	Basal cell carcinoma	1	Non-serious	Unknown	No	Resolved
		Squamous cell carcinoma	1	Non-serious	421	No	Resolved

All cases of secondary malignancies reported in the above Study MMY2001 were considered causally unrelated to Carvykti. The lentiviral vector to be used in the manufacture of Carvykti is a replication-incompetent and self-inactivating vector manufactured using a third-generation packaging system. Given these findings, the risk of insertional mutagenesis is expected to be low. Given these points, the risk of secondary malignancies associated with Carvykti should be low. Thus, aggressive testing for secondary malignancies in the post-market setting is not necessary at present. However, post-marketing information on secondary malignancies will be collected because the risk of secondary malignancies cannot be ruled out completely. Furthermore, as the long-term safety of Carvykti is unclear, the applicant is planning to collect information on secondary malignancies in a 15-year post-marketing study to evaluate long-term safety in patients previously treated with Carvykti in clinical studies including Study MMY2001, and will take appropriate safety measures as needed.

PMDA's view:

A relationship of secondary malignancies to the primary disease or prior chemotherapy cannot be ruled out, and the relationship of secondary malignancies to Carvykti is unclear at present. However, given that the risk of secondary malignancies associated with Carvykti cannot be ruled out completely, patients should be monitored for signs and symptoms of secondary malignancies. The applicant should continuously collect information on the risk of secondary malignancies in patients treated with Carvykti in post-marketing setting.

7.R.3 Clinical positioning and indication or performance

The proposed indication or performance for Carvykti was "Relapsed or refractory multiple myeloma. Carvykti should be used only in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody."

The proposed text in the PRECAUTIONS FOR INDICATION OR PERFORMANCE section was "Eligible patients should be selected by physicians with a full understanding of the efficacy and safety of Carvykti and of the information in the CLINICAL STUDIES section, including the prior treatments of patients enrolled in the clinical study."

Based on Sections "7.R.1 Efficacy," "7.R.2 Safety," and "7.R.4 Dosage and administration or method of use" and the following considerations, PMDA concluded that the following statements should be included in the INDICATION OR PERFORMANCE section, and that the proposed text in the PRECAUTIONS FOR INDICATION OR PERFORMANCE section is acceptable.

Indication or Performance (Underline denotes additions or revisions. Strikethrough denotes deletions.)
Relapsed or refractory multiple myeloma. Carvykti should be used only in patients meeting both of the following criteria.

- Patients who are naïve to BCMA-targeted chimeric antigen receptor T-cell infusion therapy
- ~~Carvykti should be used only in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody.~~ Patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and have experienced disease progression on the last therapy or relapse after the last therapy.

Precautions for Indication or Performance
Eligible patients should be selected by physicians with a full understanding of the efficacy and safety of Carvykti and of the information in the CLINICAL STUDIES section, including the prior treatments of patients enrolled in the clinical study.

7.R.3.1 Clinical positioning and target population

The applicant's explanation about the clinical positioning and indication or performance of Carvykti:
The treatment paradigm for MM underwent significant evolution in recent years, with the development of new therapeutic agents (*Pharmacother*. 2017; 37: 129-43). Despite the advance in therapy, MM remains incurable. All MM patients eventually relapse and become refractory to existing treatments. With each successive relapse, QOL worsens, and the response rate and the duration of response decrease. The median overall survival in patients with MM who have received at least 3 prior lines of therapy and are refractory to both immunomodulatory drugs and proteasome inhibitors is 13 months (*Leukemia.* 2017; 31: 2443-8). The reported overall response rate for approved therapies for the population of heavily pre-treated patients with relapsed or

refractory MM, is approximately 30% or less, and the reported median PFS is 3.7 to 4 months (*Lancet Oncol*. 2013; 14: 1055-66, *Leukemia.* 2017; 31: 107-114, etc.). Thus, there is a significant unmet medical need for new therapeutic options directed at alternative mechanisms of action that can achieve a better control of the disease.

Since the results of Study MMY2001 demonstrated the efficacy and safety of Carvykti in patients with relapsed or refractory MM who had received at least 3 prior lines of therapy, Carvykti will offer a new treatment option for these patients.

PMDA asked the applicant to explain whether the efficacy of Carvykti tends to differ depending on the number of prior lines of therapy and the response to the last line of prior therapy (relapsed or refractory) in patients for whom Carvykti is recommended.

The applicant's response:

Data from Study MMY2001 were analyzed for the overall response rate and the complete response rate by the number of prior lines of therapy (3, 4, ≥5) in the non-Japanese population who received Carvykti within the target dose range of 0.5×10^6 to 1.0×10^6 anti-BCMA CAR-positive viable T cells/kg (data cutoff date of February 11, 2021). The overall response rate and the complete response rate were 100% and 88.2%, respectively, in 17 patients who received 3 prior lines of therapy, 93.8% and 75.0%, respectively, in 16 patients who received 4 prior lines of therapy, and 98.4% and 79.7%, respectively, in 64 patients who received ≥5 prior lines of therapy. Efficacy data did not tend to differ depending on the number of prior lines of therapy. The overall response rate and the complete response rate by the number of prior lines of therapy (3, 4, ≥5) in the Japanese population (data cutoff date of July 22, 2021) were 100% and 50.0%, respectively, in 2 patients who received 3 prior lines of therapy, 100% and 100%, respectively, in 1 patient who received 4 prior lines of therapy, and 100% and 40.0%, respectively, in 5 patients who received ≥5 prior lines of therapy.

The response to the last line of therapy (relapsed or refractory[31)]) was investigated in Study MMY2001. Only 1 patient in the non-Japanese population relapsed after the last therapy, with the best response of stringent complete response (sCR). The overall response rates [95% CI] among patients who were refractory to the last therapy (8 in the Japanese population, 96 in the non-Japanese population) were 100.0% [63.1%, 100.0%] in the Japanese population and 97.9% [92.7%, 99.7%] in the non-Japanese population, and the complete response rates [95% CI] were 50.0% [15.7%, 84.3%] in the Japanese population and 80.2% [70.8%, 87.6%] in the non-Japanese population.

PMDA's view:

On the whole, the indication or performance for Carvykti can be established based on results from Study

[31)] The definitions of "relapsed" or "refractory" disease are shown below.
Relapsed disease: PD according to IMWG criteria, not meeting the following definition of refractory disease
Refractory disease: non-responsive to prior therapy (never achieve MR with any therapy or PD) or PD within 60 days of the last therapy

MMY2001. Meanwhile, given the inclusion criterion as to the response to the last therapy specified in the clinical study, the INDICATION OR PERFORMANCE section should clearly state that Carvykti is used in patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and have experienced disease progression on the last therapy or relapse after the last therapy.

"Eligible patients should be selected by physicians with a full understanding of the efficacy and safety of Carvykti and of the information in the CLINICAL STUDIES section, including the prior treatments of patients enrolled in the clinical study." should be included in the PRECAUTIONS FOR INDICATION OR PERFORMANCE section. The proposed text in the PRECAUTIONS FOR INDICATION OR PERFORMANCE section is acceptable.

7.R.3.2 Need for pretreatment testing for BCMA antigen expression

PMDA asked the applicant to explain the need for testing for BCMA antigen expression prior to administration of Carvykti.

The applicant's response:

Pretreatment testing for BCMA antigen expression on tumor cells is not necessary for the following reasons:

- In Study MMY2001, BCMA expression was detected by flow cytometry in all of 62 subjects evaluable for BCMA expression on tumor cells at baseline (the non-Japanese population only). In 13 studies in patients with MM, high BCMA expression was detected in all evaluable patient samples collected from either newly diagnosed MM or relapsed or refractory MM patients (*Blood Cancer J*. 2020; 10: 73). These findings suggest that there are very few MM patients with no BCMA expression on tumor cells.
- In the non-Japanese population of Study MMY2001, the overall response rate [95% CI] in 62 patients with BCMA-positive tumor cells was 98.4% [91.3%, 100%], and the overall response rate [95% CI] in 35 patients with unknown status of BCMA expression on tumor cells was 97.1% [85.1%, 99.9%]. Both groups of patients had similar efficacy results. There were no clear differences in safety as well.

PMDA's view:

The above explanation by the applicant is understandable. BCMA is universally expressed on the tumor cells of patients with relapsed or refractory MM, and Carvykti is expected to be effective even without pretreatment testing for BCMA expression. For these and other reasons, testing for BCMA antigen expression prior to administration of Carvykti is not necessary.

7.R.3.3 Patients previously treated with allogeneic hematopoietic stem cell transplant

The applicant's explanation about patients previously treated with allogeneic hematopoietic stem cell transplant (HSCT):

In Study MMY2001, 8 of 97 non-Japanese patients and 2 of 9 Japanese patients were previously treated with allogeneic HSCT. In the non-Japanese population (data cutoff date of February 11, 2021), the overall response

rates [95% CI] in 8 patients with prior allogeneic HSCT and 89 patients without prior allogeneic HSCT were 87.5% [47.3%, 99.7%] and 98.9% [93.9%, 100%], respectively. Two Japanese patients with prior allogeneic HSCT had best responses of sCR and very good partial response (VGPR).

Safety data from the non-Japanese population (data cutoff date of February 11, 2021) were analyzed. The incidences of adverse events and Grade ≥3 adverse events were both 100% in patients with (n = 8) or without (n = 89) prior allogeneic HSCT. There were no Grade ≥3 adverse events reported at a ≥25% higher incidence in patients with prior allogeneic HSCT than in patients without prior allogeneic HSCT. There were no clear differences in the incidences of adverse events of special interest, i.e., CRS and neurologic disorder. Grade ≥3 adverse events observed in the 2 Japanese patients previously treated with allogeneic HSCT were neutropenia, anaemia, and thrombocytopenia, and no serious adverse events were reported.

As described in the above, the number of treated patients with prior allogeneic HSCT is limited, and this precludes drawing a definitive conclusion on differences in the safety profile according to prior allogeneic HSCT status, based on the results of the study.

When patients receive Carvykti therapy after allogeneic HSCT, both CAR-T cells derived from the donor and CAR-T cells derived from the recipient may be present in the final product manufactured, depending on the level of engraftment of donor cells. Due to the presence of CAR-T cells derived from the donor, which are processed cells more likely to attack the recipient's tissues, in the final product, Carvykti infusion may lead to the development of graft versus host disease (GVHD) or the aggravation of GVHD after allogeneic HSCT. Thus, the following statement should be added in the PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE section: Carvykti infusion should be delayed if a patient has active GVHD after allogeneic HSCT.

PMDA's view:
Study MMY2001 showed no clear differences in the safety profile according to prior allogeneic HSCT status. However, since Carvykti infusion may aggravate active GVHD after allogeneic HSCT, the PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE section should advise that Carvykti infusion should be delayed if a patient has active GVHD. Furthermore, given that (i) there is limited clinical experience with Carvykti in patients previously treated with allogeneic HSCT at present and (ii) GVHD may occur following Carvykti infusion also in patients previously treated with allogeneic HSCT who have no active GVHD, the applicant should collect post-marketing information on the safety of Carvykti in these patients [see Section "8. Risk Analysis and Outline of the Review Conducted by PMDA"].

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

The proposed text in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section is shown below.

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis
   White blood cells including sufficient T-lymphocytes are collected.
2. Transportation of leukapheresis material
   The collected leukapheresis material is packed in a transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti
   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at ≤−120°C) until immediately before use.
4. Pretreatment before administration of Carvykti
   Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion. Adminiter cyclophosphamide 300 mg/m^2 (on the anhydrous basis) and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
   If resolution of Grade ≥3[Note)] toxicities due to the lymphodepleting chemotherapy to Grade 1[Note)] or lower takes ≥14 days, thereby resulting in delays in Carvykti dosing, the lymphodepleting chemotherapy should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting chemotherapy.
   Note) Toxicities are graded according to the NCI-CTCAE v5.0.
5. Administration of Carvykti
   Carvykti is thawed immediately before administration. The usual recommended dose range in adultsis 0.5 × 10^6 to 1.0 × 10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion (with a maximum dose of 1.0 × 10^8 CAR-positive viable T cells).

The following statements were included in the PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE section.

For the details of a series of procedures from patient leukapheresis to the administration of Carvykti, see the manual and other materials provided by the marketing authorization holder.

Pretreatment

1. Prior to Carvykti infusion, administer immunosuppressive chemotherapeutic agents, i.e., cyclophosphamide (anhydrous) and fludarabine phosphate to help promote CAR-T cell expansion. For pretreatment in the clinical study, see the CLINICAL STUDIES section.

Administration

2. Prior to Carvykti infusion, confirm that the patient's identity matches the patient information on the infusion bag label.

3. Carvykti infusion should be delayed until resolution if a patient has any of the following conditions:
   - Clinically significant active infection
   - Grade ≥3[Note)] non-haematologic toxicities of cyclophosphamide (anhydrous) and fludarabine phosphate lymphodepletion regimen, except for Grade 3[Note)] nausea, vomiting, diarrhoea, or constipation. Carvykti infusion should be delayed until resolution of these events to Grade ≤1.[Note)]

   Note) Grade is based on NCI-CTCAE v5.0.
4. Administer premedication of antihistamine and antipyretic (oral or intravenous acetaminophen) to all patients approximately 30 to 60 minutes prior to Carvykti infusion to prevent or reduce infusion reactions. Do not use corticosteroids except for life-threatening emergencies. Prepare emergency measures for severe events such as anaphylaxis.
5. Ensure that tocilizumab (genetical recombination) and emergency equipment are available prior to the infusion and during the recovery period.
6. Thaw Carvykti at 37 ± 2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thawing until completion of thawing should be no more than 15 minutes. Do not re-freeze or refrigerate thawed product.
7. Once thawed, Carvykti infusion must be completed within 2.5 hours at room temperature.
8. Inspect the Carvykti infusion bag for breaks or cracks before thawing. Do not administer if the bag is compromised.
9. When the unused suspension is disposed of, the infusion bag and its contents should be disposed of as potentially infectious waste in accordance with local guidelines.
10. Administer the entire contents of the Carvykti infusion bag.
11. Do not irradiate Carvykti as irradiation could inactivate the product.
12. Administer Carvykti using infusion sets fitted with an in-line filter. Do not use a leukocyte-depleting filter.
13. Prime the tubing of the infusion set with normal saline prior to Carvykti infusion. After the entire content of the Carvykti infusion bag is infused, rinse the infusion bag with normal saline to ensure that as many cells as possible are infused into the patient.
14. Gently mix the contents of the bag during Carvykti infusion to disperse cell clumps.

Based on Sections "7.R.1 Efficacy," "7.R.2 Safety," and "7.R.3 Clinical positioning and indication or performance" and the following considerations, PMDA concluded that the proposed text in the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE sections should be modified as follows.

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

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis

   Non-mobilized peripheral blood mononuclear cells ~~White blood cells including sufficient T lymphocytes~~

are collected by leukapheresis.

2. Transportation of leukapheresis material

   The collected leukapheresis material is packed in a transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti

   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at ≤−120°C) until immediately before use.

4. Pretreatment before administration of Carvykti

   Check the patient's condition by blood tests etc. Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion.

   Administer cyclophosphamide 300 mg/m^2(on the anhydrous basis) intravenously once daily for 3 days and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.

   ~~If resolution of Grade ≥3[Note)] toxicities due to the lymphodepleting chemotherapy to Grade 1[Note)] or lower takes ≥14 days, thereby resulting in delays in Carvykti dosing, the lymphodepleting chemotherapy should be re-administered after a minimum of 21 days following the first dose of the first lymphodepleting chemotherapy.~~

   ~~Note) Toxicities are graded according to the NCI-CTCAE v5.0.~~

5. Administration of Carvykti

   Carvykti is thawed immediately before administration. The usual ~~recommended dose range~~ target dose in adults is 0.75 × 10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion at a rate of ≤7 mL/min. The acceptable dose range is 0.5 × 10^6 to 1.0 × 10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0 × 10^8 CAR-positive viable T cells). Do not re-administer Carvykti.

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

For the details of a series of procedures from patient leukapheresis to the administration of Carvykti, see the manual and other materials provided by the marketing authorization holder.

Lymphodepleting chemotherapy or Carvykti infusion should be delayed until resolution if a patient has any of the following conditions:

- Unresolved serious adverse events including events from preceding chemotherapies (e.g., pulmonary disorders, cardiac disorders, hypotension)
- Active infection, inflammatory disorders
- Active graft versus host disease (GVHD)

Pretreatment

1. Prior to Carvykti infusion, administer immunosuppressive chemotherapeutic agents, i.e., cyclophosphamide (anhydrous) and fludarabine phosphate to help promote CAR-T cell expansion. For pretreatment in the clinical study, see the CLINICAL STUDIES section.

Administration <u>of Carvykti</u>

2. Prior to Carvykti infusion, confirm that the patient's identity matches the patient information on the infusion bag label.

~~3. Carvykti infusion should be delayed until resolution if a patient has any of the following conditions:~~

- ~~Clinically significant active infection~~
- ~~Grade ≥3[Note)] non-haematologic toxicities of cyclophosphamide (anhydrous) and fludarabine phosphate lymphodepletion regimen, except for Grade 3[Note)] nausea, vomiting, diarrhoea, or constipation. Carvykti infusion should be delayed until resolution of these events to Grade ≤1.[Note)]~~

~~Note) Grade is based on NCI-CTCAE v5.0.~~

3. Administer premedication of antihistamine and antipyretic (oral or intravenous acetaminophen) to all patients approximately 30 to 60 minutes prior to Carvykti infusion to prevent or reduce infusion reactions. Do not use corticosteroids except for life-threatening emergencies. Prepare emergency measures for severe events such as anaphylaxis.
4. Ensure that there is immediate access to tocilizumab (genetical recombination) ~~and emergency equipment are available prior to the infusion and during the recovery period.~~for the emergency treatment of cytokine release syndrome.
5. Thaw Carvykti at 37 ± 2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thawing until completion of thawing should be no more than 15 minutes. Do not re-freeze or refrigerate thawed product.
6. Once thawed, Carvykti infusion must be completed within 2.5 hours at room temperature.
7. Inspect the Carvykti infusion bag for breaks or cracks before thawing. Do not administer if the bag is compromised.
8. When the unused suspension is disposed of, the infusion bag and its contents should be disposed of as potentially infectious waste in accordance with local guidelines.
9. Administer the entire contents of the Carvykti infusion bag.
10. Do not irradiate Carvykti ~~as irradiation could inactivate the product~~.
11. Administer Carvykti ~~using infusion sets fitted with~~ via an in-line filter. Do not use a leukocyte-depleting filter.
12. Prime the tubing of the infusion set with normal saline prior to Carvykti infusion. After the entire content of the Carvykti infusion bag is infused, rinse the infusion bag with normal saline to ensure that as many cells as possible are infused into the patient.
13. Gently mix the contents of the bag during Carvykti infusion to disperse cell clumps.

7.R.4.1 LD chemotherapy regimen

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

LD chemotherapy regimen

The rationale for the LD chemotherapy regimen is shown below.

- LD chemotherapy before CAR T-cell therapy including Carvykti is expected to suppress host immune system, resulting in the engraftment of CAR-positive viable T cells and increased CAR T-cell activity and persistence (Chimeric Antigen Receptor T-Cell Therapies for Cancer. Elsevier; 2020. p29-44, https://lymphomahub.com/medical-information/lymphodepletion-optimization-for-car-t-cell-therapy [last accessed on March 7, 2022]).
- In a clinical study in patients with diffuse large B-cell lymphoma (DLBCL), cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 were administered once per day for 3 days as LD chemotherapy, and a single dose of anti-CD19 CAR T-cells was administered 5 days after the start of LD chemotherapy. Anti-tumor activity was demonstrated, and there were no safety problems (*Molecular Therapy*. 2014; 22: S295, *J Clin Oncol*. 2017; 35: 1803-13).
- Study MMY2001 demonstrated the efficacy and safety of Carvykti preceded by the LD chemotherapy regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days in patients with relapsed or refractory MM including Japanese patients.

Administration of LD chemotherapy

In Study MMY2001, the criteria for starting LD chemotherapy included preserved bone marrow, cardiac, hepatic, and renal functions; no active infection; and no prior therapy (including bridging therapy) within the specified timeframe.[13)]

In Study MMY2001, if Carvykti infusion was delayed due to non-hematologic toxicities of LD chemotherapy, LD chemotherapy was to be re-administered prior to Carvykti infusion because the lymphodepleting effect of LD chemotherapy was potentially attenuated.[32)] However, LD chemotherapy was not re-administered in any patient.

The DOSAGE AND ADMINISTRATION OR METHOD OF USE section will specify the rule for repeating LD chemotherapy in order to ensure the patient's safety and lymphodepletion in the event of Grade ≥3 non-hematologic toxicities due to LD chemotherapy in the post-marketing setting.

PMDA's view:

The applicant's explanation about the LD chemotherapy regimen is understandable.

[32)] If resolution of Grade ≥3 toxicities (non-hematologic toxicities except for Grade 3 nausea, vomiting, diarrhea, or constipation) took >14 days after the first dose of LD chemotherapy, Carvykti infusion was to be administered after a minimum of 21 days following the first dose of LD chemotherapy. LD chemotherapy was to be re-administered prior to Carvykti infusion.

Patients eligible for Carvykti therapy may receive anti-cancer treatment (bridging therapy) to maintain disease stability while Carvykti manufacturing is underway after leukapheresis. For this and other reasons, the DOSAGE AND ADMINISTRATION OR METHOD OF USE section should clearly state “Check the patient’s condition by blood tests etc. and then start LD chemotherapy according to the patient’s condition" if LD chemotherapy is administered, including but not limited to, to facilitate the engraftment of the infused CAR-T cells. Information on the rule for repeating LD chemotherapy should be provided appropriately to healthcare professionals using information materials.

7.R.4.2 Dosing regimen of Carvykti

The applicant’s explanation about the rationale for the dosing regimen of Carvykti:

For the following reasons, the proposed dosage and administration or method of use was “The usual recommended dose range in adults is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0×10^8 CAR-positive viable T cells) administered as a single intravenous infusion.”

- The dose used in the phase Ib part of Study MMY2001 was based on the Legend-2 study[33)] conducted in China. The number of CAR-positive viable T cells infused for 74 subjects from the Legend-2 study ranged from 0.07 to 2.10×10^6 CAR-positive viable T cells/kg. Given the incidence of CRS by dose range in this study, the incidence of high-Grade CRS can be reduced with a target dose of 0.75×10^6 CAR-positive viable T cells/kg with a maximum dose of 1.0×10^6 CAR-positive viable T cells/kg. While the dose was split into more than 1 infusion in 65 of the 74 subjects in the Legend-2 study, the remaining 9 subjects received a single infusion. Since there were no particular differences in safety and efficacy between the split doses and single dose, single dose was proposed.
- In the phase Ib part of Study MMY2001, the median number of CAR-positive viable T cells infused (range) was 0.722×10^6 CAR-positive viable T cells/kg ($0.52\text{-}0.89 \times 10^6$ CAR-positive viable T cells/kg). The results of the phase Ib part demonstrated the tolerability of Carvykti. The overall response rate as assessed by the IRC [95% CI] was 100% [88.1%, 100%], and the median time to first response (range) was 0.95 months (0.9-2.8 months). The dose used in the phase Ib part was selected also in the phase II part, in which the overall response rate in the entire non-Japanese population was 96.9%, showing favorable efficacy (data cutoff date of September 1, 2020). The overall response rate in the Japanese population was 100% (data cutoff date of July 22, 2021), which was similar to that in the non-Japanese population. Safety data showed that events such as CRS were common, but were largely manageable.

Given the characteristics of cells, the number of CAR-positive viable T cells actually administered is considered to vary within the acceptable range established for the control of the finished product during manufacturing. Since the results of Study MMY2001 were obtained from patients treated with the target dose of Carvykti, the target dose will be specified based on the dosing regimen used in Study MMY2001, and “a recommended dose range” will be deleted. The revised text is shown below.

[33)] An open-label, single-arm, multicenter phase I study to evaluate the safety and efficacy of Carvykti in patients with relapsed or refractory MM.

Carvykti is thawed immediately before administration. The usual ~~recommended dose range~~ target dose in adults is 0.75×10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion. The acceptable dose range is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0×10^8 CAR-positive viable T cells).

PMDA's view:

The above explanation by the applicant is understandable. The applicant's response (The target dose of Carvykti will be specified in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section, based on the dosing regimen used in Study MMY2001) is appropriate.

7.R.4.3 Infusion rate of Carvykti

PMDA asked the applicant to explain the need to specify the infusion rate of Carvykti in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section.

The applicant's explanation:

At the start of Study MMY2001, infusion of the specified amount per infusion bag was to be completed within 30 minutes of thawing. Then, as longer stability was demonstrated, the infusion rate was changed so that Carvykti is to be administered via gravity. Thus, the infusion rate of Carvykti was not specified. Although the start and end times of infusion were recorded, the exact infusion rate of Carvykti could not be calculated because the infusion time included flushing with normal saline. When more than one bag of Carvykti was infused, the start and end times of infusion were recorded for each bag. The sum of these periods was calculated as the infusion time. The median infusion time (range) was 19 minutes (5-71 minutes) in the non-Japanese population (97 subjects) and 11 minutes (7-22 minutes) in the Japanese population (9 subjects). The median infused volume (range) was 70 mL (30-140 mL) in the non-Japanese population and 30 mL (30-70 mL) in the Japanese population. Four patients received more than one bag of Carvykti (2 non-Japanese patients received 2 bags containing 70 mL of cell suspension and the remaining 2 non-Japanese patients received 2 bags containing 30 mL of cell suspension).

For the following and other reasons, there is no need to specify the infusion rate of Carvykti, and Carvykti should be administered via gravity as in the clinical study.

- As to the infusion rate, when the maximum dose of 70 mL per bag is administered, the dose of potassium administered is up to 125 mg (approximately 3.2 mEq, the maximum concentration of 45.8 mEq/L). The package insert for potassium chloride for intravenous infusion states that the maximum allowable infusion rate of potassium chloride is 20 mEq/hour, which corresponds to the infusion rate of Carvykti of 7.2 mL/min. Given the risk of hyperkalaemia due to a rapid infusion rate, the incidence of hyperkalaemia in Study MMY2001 was investigated. Hyperkalaemia occurred in 3 subjects. A causal relationship to Carvykti could not be ruled out for 1 of the 3 cases, but the event occurred 72 days after Carvykti infusion, which was not considered due to a rapid infusion of Carvykti.

- The correlation between the infusion rate (mL/min) of dimethyl sulfoxide (DMSO) used in transplantation and side effects of DMSO in patients with myeloma or lymphoma was analyzed (1651 patients). There were no significant differences between patients in the highest quartile and other quartiles of infusion rate (*TRANSFUSION*. 2014; 54: 2514-22).

PMDA's view:
The analysis in the clinical study provided only limited data. There is the risk of hyperkalaemia due to a rapid infusion rate of Carvykti. To avoid a rapid rise in blood potassium levels following Carvykti infusion, the maximum infusion rate of Carvykti should be specified in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section, in view of the maximum allowable infusion rate specified in the package insert for potassium chloride for intravenous infusion.

PMDA requested the applicant to specify the maximum infusion rate of Carvykti in the DOSAGE AND ADMINISTRATION OR METHOD OF USE section. The applicant responded that the DOSAGE AND ADMINISTRATION OR METHOD OF USE section will state that Carvykti should be administered as a single intravenous infusion at a rate of ≤7 mL/min.

PMDA accepted the applicant's response.

7.R.4.4 Re-administration of Carvykti

In Study MMY2001, subjects could be considered for retreatment with Carvykti if the following criteria were met: PD after best response of MR or better and at least 6 months between the first Carvykti infusion and detection of PD. PMDA asked the applicant to explain if retreatment with Carvykti is recommended.

The applicant's explanation:
In Study MMY2001, 1 non-Japanese subject received retreatment with Carvykti. PD was the best response to retreatment. The retreated subject experienced Grade 3 and 4 neutropenia, which was assessed as causally related to Carvykti. No serious adverse events, CRS, or neurologic disorders were reported.

The limited data on retreatment with Carvykti preclude risk-benefit assessment, and retreatment with Carvykti cannot be recommended. The package insert will include a precaution that due to the limited data on retreatment with Carvykti, its efficacy and safety have not been established.

PMDA's discussion:
Retreatment with Carvykti cannot be recommended at present due to very limited clinical experience with retreatment. Because this information is important, the DOSAGE AND ADMINISTRATION OR METHOD OF USE section should state that retreatment with Carvykti is no allowed. As the information in relation to not recommending retreatment with Carvykti, patients with prior treatment with CAR-T therapy directed at any target or prior therapy that is targeted at BCMA were excluded from Study MMY2001. Given this point, the

INDICATION OR PERFORMANCE section should clearly state that patients previously treated with BCMA-targeted CAR T-cell infusion therapy are not eligible for Carvykti.

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

The applicant's explanation about a post-marketing surveillance plan for Carvykti:
The applicant is planning all-case post-marketing surveillance covering all patients with relapsed or refractory MM treated with Carvykti to evaluate the safety of Carvykti in clinical use.

In light of the incidences of adverse events reported in Study MMY2001 and other data, the safety specification for the surveillance will include "CRS (including HLH)," "neurologic disorders (including ICANS and other neurotoxicities)," "prolonged cytopenia (excluding anaemia)," "serious infections," and "secondary malignancies" as expected risks associated with the use of Carvykti in the post-marketing setting, and "long-term safety," "use in pregnant and breast feeding women," "use in patients with pre-existing autoimmune disease," "use in patients with pre-existing neurodegenerative disorders," "use in patients with active CNS involvement by malignancy," and "use in patients with chronic HIV/HBV/HCV infection" as missing information.

A planned sample size of 300 patients has been chosen, taking account of the incidences of the risks included in the safety specification in Study MMY2001.

An observation period of at least 5 years (up to 8 years) for each patient has been chosen, taking account of the importance of a long-term follow-up. Long-term safety data regarding secondary malignancies will be separately collected for 15 years in a follow-up study in patients previously treated with Carvykti in clinical studies including Study MMY2001, and appropriate safety measures will be taken as needed.

PMDA's view:
The safety information from Japanese patients treated with Carvykti is very limited. For this and other reasons, the applicant should conduct post-marketing surveillance covering all patients treated with Carvykti, collect information, and promptly provide the obtained safety information to healthcare professionals in clinical practice.

Based on the considerations in Section "7.R.2 Safety," "hypersensitivity," "hypogammaglobulinaemia," and "TLS" should also be added to the safety specification for the all-case surveillance, and "prolonged cytopenia (excluding anaemia)" should be replaced with "prolonged cytopenia." Based on the considerations in Section "7.R.3.3 Patients previously treated with allogeneic HSCT," "graft versus host disease" should be included in the safety specification. Further, "use in patients with active CNS involvement by malignancy" should be deleted from the safety specification. Because no patients with CNS involvement by MM received Carvykti in Study MMY2001, Carvykti is not recommended in these patients.

The planned sample size and observation period as proposed by the applicant are acceptable.

The details of post-marketing use-results survey will be finalized, taking also account of comments from the Expert Discussion concerning the safety assessment of Carvykti.

9. Adverse Events Observed in Clinical Studies

Among clinical study data submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data." Main adverse events other than deaths are described below.

9.1 Global phase Ib/II study (Study MMY2001)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to Carvykti could not be ruled out occurred in 96 of 97 subjects (99.0%) in the non-Japanese population, but such events occurred in all subjects in the Japanese population. Table 36 shows adverse events reported by ≥10% of subjects in the entire non-Japanese population or Japanese population.

Table 36. Adverse events reported by ≥10% of subjects in the entire non-Japanese population or Japanese population (Study MMY2001)

	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
SOC PT (MedDRA/J ver.23.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	9 (100)	8 (88.9)	29 (100)	29 (100)	68 (100)	68 (100)	97 (100)	97 (100)
Blood and lymphatic system disorders								
Neutropenia	8 (88.9)	8 (88.9)	29 (100)	29 (100)	64 (94.1)	63 (92.6)	93 (95.9)	92 (94.8)
Thrombocytopenia	7 (77.8)	7 (77.8)	25 (86.2)	20 (69.0)	52 (76.5)	38 (55.9)	77 (79.4)	58 (59.8)
Anaemia	6 (66.7)	6 (66.7)	22 (75.9)	15 (51.7)	57 (83.8)	51 (75.0)	79 (81.4)	66 (68.0)
Leukopenia	4 (44.4)	4 (44.4)	20 (69.0)	20 (69.0)	40 (58.8)	39 (57.4)	60 (61.9)	59 (60.8)
Lymphopenia	0	0	16 (55.2)	15 (51.7)	35 (51.5)	33 (48.5)	51 (52.6)	48 (49.5)
Febrile neutropenia	3 (33.3)	3 (33.3)	1 (3.4)	1 (3.4)	9 (13.2)	8 (11.8)	10 (10.3)	9 (9.3)
Hypofibrinogenaemia	2 (22.2)	2 (22.2)	0	0	11 (16.2)	1 (1.5)	11 (11.3)	1 (1.0)
Lymphocytosis	2 (22.2)	1 (11.1)	0	0	1 (1.5)	0	1 (1.0)	0
Immune system disorders								
CRS	8 (88.9)	0	27 (93.1)	3 (10.3)	65 (95.6)	2 (2.9)	92 (94.8)	5 (5.2)
Hypogammaglobulinaemia	1 (11.1)	0	1 (3.4)	0	11 (16.2)	2 (2.9)	12 (12.4)	2 (2.1)
Metabolism and nutrition disorders								
Hypokalaemia	2 (22.2)	1 (11.1)	3 (10.3)	0	17 (25.0)	2 (2.9)	20 (20.6)	2 (2.1)
Hypophosphataemia	0	0	6 (20.7)	3 (10.3)	24 (35.3)	4 (5.9)	30 (30.9)	7 (7.2)
Decreased appetite	1 (11.1)	0	3 (10.3)	0	25 (36.8)	1 (1.5)	28 (28.9)	1 (1.0)
Fluid retention	1 (11.1)	0	0	0	0	0	0	0
Hypocalcaemia	0	0	2 (6.9)	0	29 (42.6)	3 (4.4)	31 (32.0)	3 (3.1)
Hypoalbuminaemia	0	0	6 (20.7)	0	21 (30.9)	1 (1.5)	27 (27.8)	1 (1.0)
Hypomagnesaemia	0	0	1 (3.4)	0	12 (17.6)	0	13 (13.4)	0
Hyponatraemia	0	0	2 (6.9)	0	20 (29.4)	4 (5.9)	22 (22.7)	4 (4.1)
Gastrointestinal disorders								
Diarrhoea	2 (22.2)	0	10 (34.5)	0	19 (27.9)	1 (1.5)	29 (29.9)	1 (1.0)
Nausea	3 (33.3)	0	6 (20.7)	0	21 (30.9)	1 (1.5)	27 (27.8)	1 (1.0)
Vomiting	3 (33.3)	0	5 (17.2)	0	14 (20.6)	0	19 (19.6)	0
Constipation	0	0	7 (24.1)	0	14 (20.6)	0	21 (21.6)	0
Infections and infestations								
Upper respiratory tract infection	1 (11.1)	0	9 (31.0)	0	6 (8.8)	1 (1.5)	15 (15.5)	1 (1.0)
Bacteraemia	1 (11.1)	0	0	0	1 (1.5)	0	1 (1.0)	0
General disorders and administration site conditions								
Fatigue	1 (11.1)	1 (11.1)	6 (20.7)	1 (3.4)	30 (44.1)	4 (5.9)	36 (37.1)	5 (5.2)
Chills	0	0	3 (10.3)	0	17 (25.0)	0	20 (20.6)	0
Pyrexia	0	0	2 (6.9)	0	18 (26.5)	0	20 (20.6)	0
Oedema peripheral	0	0	3 (10.3)	0	14 (20.6)	0	17 (17.5)	0
Malaise	1 (11.1)	1 (11.1)	2 (6.9)	0	1 (1.5)	0	3 (3.1)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	1 (11.1)	0	4 (13.8)	0	11 (16.2)	0	15 (15.5)	0
Back pain	1 (11.1)	0	1 (3.4)	0	9 (13.2)	0	10 (10.3)	0
Pain in extremity	0	0	4 (13.8)	0	10 (14.7)	0	14 (14.4)	0
Investigations								
Aspartate aminotransferase increased	3 (33.3)	3 (33.3)	10 (34.5)	2 (6.9)	18 (26.5)	3 (4.4)	28 (28.9)	5 (5.2)
Alanine aminotransferase increased	2 (22.2)	1 (11.1)	9 (31.0)	2 (6.9)	15 (22.1)	1 (1.5)	24 (24.7)	3 (3.1)
Blood alkaline phosphatase increased	0	0	2 (6.9)	1 (3.4)	10 (14.7)	2 (2.9)	12 (12.4)	3 (3.1)

	n (%)							
	Japanese population		Non-Japanese population					
	N = 9		Phase Ib N = 29		Phase II N = 68		Phase Ib + Phase II N = 97	
SOC PT (MedDRA/J ver.23.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood lactate dehydrogenase increased	1 (11.1)	0	0	0	12 (17.6)	0	12 (12.4)	0
Gamma-glutamyltransferase increased	1 (11.1)	1 (11.1)	2 (6.9)	1 (3.4)	11 (16.2)	5 (7.4)	13 (13.4)	6 (6.2)
Nervous system disorders								
Headache	3 (33.3)	0	5 (17.2)	0	14 (20.6)	0	19 (19.6)	0
Dizziness	0	0	4 (13.8)	0	14 (20.6)	0	18 (18.6)	0
ICANS	0	0	3 (10.3)	1 (3.4)	13 (19.1)	1 (1.5)	16 (16.5)	2 (2.1)
Somnolence	1 (11.1)	0	0	0	1 (1.5)	1 (1.5)	1 (1.0)	1 (1.0)
Respiratory, thoracic and mediastinal disorders								
Cough	0	0	8 (27.6)	0	26 (38.2)	0	34 (35.1)	0
Dyspnoea	0	0	3 (10.3)	0	9 (13.2)	0	12 (12.4)	0
Nasal congestion	0	0	4 (13.8)	0	11 (16.2)	0	15 (15.5)	0
Vascular disorders								
Hypotension	0	0	2 (6.9)	0	13 (19.1)	2 (2.9)	15 (15.5)	2 (2.1)
Hypertension	1 (11.1)	0	3 (10.3)	1 (3.4)	15 (22.1)	5 (7.4)	18 (18.6)	6 (6.2)
Embolism	1 (11.1)	0	0	0	0	0	0	0
Psychiatric disorders								
Insomnia	0	0	2 (6.9)	0	11 (16.2)	0	13 (13.4)	0
Cardiac disorders								
Sinus tachycardia	0	0	1 (3.4)	0	12 (17.6)	1 (1.5)	13 (13.4)	1 (1.0)

In the non-Japanese population, serious adverse events occurred in 11 of 29 subjects (37.9%) in the phase Ib part, 42 of 68 subjects (61.8%) in the phase II part, and 53 of 97 subjects (54.6%) in the phase Ib + II parts. Serious adverse events occurred in 1 of 9 subjects (11.1%) in the Japanese population. Serious adverse events reported by ≥2 subjects in the entire non-Japanese population were CRS (20 subjects [20.6%]); pneumonia, sepsis, and ICANS (5 subjects each [5.2%]); febrile neutropenia (4 subjects [4.1%]); parkinsonism, hypoxemia, thrombocytopenia, and mental status changes (3 subjects each [3.1%]); and rhinovirus infection, neurotoxicity, confusional state, pyrexia, and acute kidney injury (2 subjects each [2.1%]). A causal relationship to Carvykti could not be ruled out for any of the following events: CRS (20 subjects); ICANS (5 subjects); febrile neutropenia and sepsis (4 subjects each); parkinsonism and mental status changes (3 subjects each); thrombocytopenia, neurotoxicity, and pneumonia (2 subjects each); and rhinovirus infection, hypoxia, confusional state, pyrexia, and acute kidney injury (1 subject each). Serious adverse events observed in the Japanese population were neutropenia, thrombocytopenia, fatigue, and CRS (1 subject each [11.1%]). A causal relationship to Carvykti could not be ruled out for any of those events.

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 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 5.3.5.2.1-3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that Carvykti has a certain level of efficacy in the treatment of relapsed or refractory multiple myeloma, and that Carvykti has acceptable safety in view of its benefits. PMDA considers that offering Carvykti as a new treatment option for patients with MM has its significance.

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

Review Report (2)

July 13, 2022

Product Submitted for Approval

Brand Name	Carvykti Suspension for Intravenous Infusion
Non-proprietary Name	Ciltacabtagene autoleucel
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 6, 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

Based on the considerations in Section "7.R.1 Efficacy" in the Review Report (1), PMDA has concluded that the submitted data demonstrate a certain level of efficacy of Carvykti in patients with relapsed or refractory MM because, among others, the primary endpoint of the overall response rate was greater than the pre-specified threshold in Study MMY2001.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

Based on the considerations in Section "7.R.2 Safety" in the Review Report (1), PMDA has concluded that adverse events that require particular attention following administration of Carvykti are CRS, HLH, neurologic disorders, infections, cytopenia, hypersensitivity, hypogammaglobulinaemia, and TLS. Patients should be monitored for signs and symptoms of these adverse events following administration of Carvykti.

Carvykti is tolerable as long as physicians with adequate knowledge of and experience in the treatment of MM take appropriate measures, such as monitoring for and management of adverse events, at medical institutions with adequate facilities for the management of the above adverse events.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Clinical positioning and indication or performance

Based on the considerations in Section "7.R.3 Clinical positioning and indication or performance" in the Review Report (1) and given that Study MMY2001 included patients with stable disease (SD) (who never achieved MR with any therapy) as patients non-responsive to prior therapy and that the following results were obtained from these patients, PMDA has concluded that the indication or performance should be modified so that these patients are eligible for treatment with Carvikti.

- Five subjects in the non-Japanese population had SD, and the overall response rate [95% CI] was 100% [47.8%, 100%].
- Two subjects in the Japanese population had SD, and their overall best responses were sCR and VGPR.

Based on the above, PMDA has concluded that the following statements should be included in the INDICATION OR PERFORMANCE AND PRECAUTIONS FOR INDICATION OR PERFORMANCE sections.

Indication or Performance

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

- Patients who are naïve to BCMA-targeted chimeric antigen receptor T-cell infusion therapy
- Patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and who have failed to respond to or have relapsed after the last therapy

Precautions for Indication or Performance

Eligible patients should be selected by physicians with a full understanding of the efficacy and safety of Carvykti and of the information in the CLINICAL STUDIES section, including the prior treatments of patients enrolled in the clinical study.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

PMDA requested the applicant to include the above statements in the INDICATION OR PERFORMANCE and PRECAUTIONS FOR INDICATION OR PERFORMANCE sections. The applicant appropriately responded to the request, and PMDA accepted the applicant's response.

1.4 Dosage and administration or method of use

Based on the considerations in Section "7.R.4 Dosage and administration or method of use" in the Review

Report (1), PMDA has concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE sections, as shown in Section 7.R.4 in the Review Report (1).

Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to 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 transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti
   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at ≤−120°C) until immediately before use.
4. Pretreatment before administration of Carvykti
   Check the patient's condition by blood tests etc. Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion.
   Administer cyclophosphamide 300 mg/m^2 (on the anhydrous basis) intravenously once daily for 3 days and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient's condition.
5. Administration of Carvykti
   Carvykti is thawed immediately before administration. The usual target dose in adults is 0.75×10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion at a rate of ≤7 mL/min. The acceptable dose range is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0×10^8 CAR-positive viable T cells). Do not re-administer Carvykti.

Precautions for Dosage and Administration or Method of Use

For the details of a series of procedures from patient leukapheresis to the administration of Carvykti, see the manual and other materials provided by the marketing authorization holder.

Lymphodepleting chemotherapy or Carvykti infusion should be delayed until resolution if a patient has any of the following conditions:

- Unresolved serious adverse events including events from preceding chemotherapies (e.g., pulmonary disorders, cardiac disorders, hypotension)
- Active infection, inflammatory disorders
- Active graft versus host disease (GVHD)

Pretreatment

1. Prior to Carvykti infusion, administer immunosuppressive chemotherapeutic agents, i.e., cyclophosphamide and fludarabine phosphate to help promote CAR-T cell expansion. For pretreatment in the clinical study, see the CLINICAL STUDIES section.

Administration of Carvykti

2. Prior to Carvykti infusion, confirm that the patient's identity matches the patient information on the infusion bag label.
3. Administer premedication of antihistamine and antipyretic (oral or intravenous acetaminophen) to all patients approximately 30 to 60 minutes prior to Carvykti infusion to prevent or reduce infusion reactions. Do not use corticosteroids except for life-threatening emergencies. Prepare emergency measures for severe events such as anaphylaxis.
4. Ensure that there is immediate access to tocilizumab (genetical recombination) for the emergency treatment of cytokine release syndrome.
5. Thaw Carvykti at 37 ± 2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thawing until completion of thawing should be no more than 15 minutes. Do not re-freeze or refrigerate thawed product.
6. Once thawed, Carvykti infusion must be completed within 2.5 hours at room temperature.
7. Inspect the Carvykti infusion bag for breaks or cracks before thawing. Do not administer if the bag is compromised.
8. If the unused suspension is disposed of, the infusion bag together with its contents should be disposed of as potentially infectious waste in accordance with local guidelines.
9. Administer the entire contents of the product bag.
10. Do not irradiate Carvykti.
11. Administer Carvykti via an in-line filter. Do not use a leukocyte-depleting filter.
12. Prime the tubing of the infusion set with normal saline prior to Carvykti infusion. After the entire content of the Carvykti infusion bag is infused, rinse the infusion bag with normal saline to ensure that as many cells as possible are infused into the patient.
13. Gently mix the contents of the bag during Carvykti infusion to disperse cell clumps.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

PMDA requested the applicant to include the above statements in the DOSAGE AND ADMINISTRATION OR METHOD OF USE and PRECAUTIONS FOR DOSAGE AND ADMINISTRATION OR METHOD OF USE sections. The applicant appropriately responded to the request, and PMDA accepted the applicant’s response.

1.5 Post-marketing surveillance plan (draft)

At the time of submission of the application, the applicant proposed a plan of post-marketing surveillance

covering all patients treated with Carvykti to evaluate the safety and other aspects of Carvykti in clinical use. The planned sample size was 300 patients. The planned observation period was up to 8 years.

PMDA's conclusion:
Based on the considerations in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" in the Review Report (1), "hypersensitivity," "hypogammaglobulinaemia," and "TLS" should be added to the safety specification for the post-marketing surveillance, and "prolonged cytopenia (excluding anaemia)" should be replaced with "prolonged cytopenia. Based on the considerations in Section "7.R.3.3 Patients previously treated with allogeneic HSCT," "aggravation of graft versus host disease" should also be included in the safety specification. Further, "use in patients with active CNS involvement by malignancy" should be deleted from the safety specification." Because no patients with CNS involvement by MM received Carvykti in Study MMY2001, Carvykti is not recommended in these patients.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

In light of the results of the Expert Discussion, PMDA requested the applicant to modify the post-marketing surveillance plan. The applicant submitted an outline of post-marketing surveillance plan (draft) presented in Table 37, and PMDA accepted it.

Table 37. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety and other aspects of Carvykti in clinical use.
Survey method	All-case surveillance The applicant will obtain the data on the target population from the data accrued 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	300 patients
Main survey items	Safety specification CRS (including HLH), neurologic events (including ICANS and other neurotoxicities), prolonged cytopenia, infections, hypersensitivity, hypogammaglobulinaemia, TLS, secondary malignancies, aggravation of graft versus host disease, long-term safety, use in pregnant or breastfeeding women, use in patients with pre-existing autoimmune disease, use in patients with pre-existing neurodegenerative disorders, use in patients with chronic HIV/HBV/HCV infection

1.6 Others

1.6.1 Proposed product shelf-life

The applicant's explanation about the product shelf-life:
As with [redacted], no changes in quality attributes were observed throughout the testing period in [redacted] manufactured [redacted].

Based on the above, a shelf-life of 9 months is proposed for the finished product when stored in an EVA freezing bag at ≤−120°C.

PMDA accepted the applicant's explanation.

1.6.2 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (Notification Nos. 1105-1 and 1105-2, both dated November 5, 2014, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW and the Counselor of Minister's Secretariat, MHLW, respectively), PMDA has concluded that Carvykti need not be designated as a specified regenerative medical product for the following reasons: All raw materials of human or animal origin used in the manufacture of Carvykti conform to the Standards for Biological Ingredients, and the risk of infections is considered very low.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication or performance and dosage and administration or method of use as shown below, with the following approval conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated in the post-marketing setting. Since the product has been designated as an orphan regenerative medical product, the re-examination period is 10 years. The product need not be designated as a specified regenerative medical product.

Indication or Performance

Relapsed or refractory multiple myeloma. Carvykti should be used only in patients meeting both of the following criteria.

- Patients who are naïve to BCMA-targeted chimeric antigen receptor T-cell infusion therapy
- Patients who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody and who have failed to respond to or have relapsed after the last therapy

Dosage and Administration or Method of Use

Process from leukapheresis at medical institution to transportation to manufacturing facility

1. Leukapheresis

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2. Transportation of leukapheresis material

   The collected leukapheresis material is packed in a transport cooler kept at 2℃ to 8℃ and transported to the manufacturing facility of Carvykti.

Process from acceptance at the medical institution to administration of Carvykti

3. Receipt and storage of Carvykti

   Carvykti is received in a frozen condition and cryopreserved in the vapor phase of liquid nitrogen (at

≤−120°C) until immediately before use.

4. Pretreatment before administration of Carvykti

   Check the patient's condition by blood tests etc. Start the following lymphodepleting chemotherapy 5 to 7 days prior to Carvykti infusion.

   Administer cyclophosphamide 300 mg/m^2 (on the anhydrous basis) intravenously once daily for 3 days and fludarabine phosphate 30 mg/m^2 intravenously once daily for 3 days. The dose may be reduced according to the patient’s condition.

5. Administration of Carvykti

   Carvykti is thawed immediately before administration. The usual target dose in adults is 0.75×10^6 CAR-positive viable T cells/kg (body weight) administered as a single intravenous infusion at a rate of ≤7 mL/min. The acceptable dose range is 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg (body weight) (with a maximum dose of 1.0×10^8 CAR-positive viable T cells). Do not re-administer Carvykti.

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. Because only a limited number of Japanese patients participated in the clinical study of the product, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product until data from a specified number of patients have been collected, in order to understand the characteristics of patients using the product and to collect safety and efficacy data as early as possible, thereby taking necessary measures to ensure the proper use of the product.

Appendix

List of Abbreviations

AAV	adeno-associated virus
[redacted]	[redacted]
anti-BCMA CAR	anti-BCMA chimeric antigen receptor
anti-CD19 CAR	anti-CD19 chimeric antigen receptor
Application	Application for marketing approval
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the blood concentration-time curve
$AUC_{0\text{-}28d}$	area under the curve of the transgene level from time of dose to 28 days postinfusion
$AUC_{0\text{-}6m}$	area under the curve of the transgene level from time of dose to 6 months postinfusion
AUC_{last}	area under the curve of the transgene level from time of dose to time of last measurable
BAV	bovine adenovirus
BCMA	B cell maturation antigen
BHV	bovine herpesvirus
BPV	bovine parvovirus
BRSV	bovine respiratory syncytial virus
BTV	bluetongue virus
BT cells	bovine turbinate cells
BVDV	bovine viral diarrhea virus
CAR	chimeric antigen receptor
CAT-T cells	cells as the active substance of the product
Carvykti	Carvykti Suspension for Intravenous Infusion
CD	cluster of differentiation
CI	confidence interval
C_{last}	last measurable transgene level
C_{max}	maximum transgene level
CMV	cytomegalovirus
CNS	central nervous system
CQA	critical quality attribute
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
DMSO	dimethyl sulfoxide
DOR	duration of response
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EPC	end of production cell
EV	enterovirus
EVA	ethylene vinyl acetate
FLC	free light chain
Fludarabine	Fludarabine Phosphate
gDNA	genomic DNA
GVHD	graft versus host disease
HAV	hepatitis A virus
HBV	hepatitis B virus

HCT-8 cells	human colon tumor cells
HCV	hepatitis C virus
HEV	hepatitis E virus
HEK293F cells	human embryonic kidney 293F
HEK293T cells	human embryonic kidney 293T
HeLa cells	human cervical cancer cells
HHV	human herpes virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPV	human papillomavirus
HSA	human serum albumin
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
HTLV	human T-cell leukemia virus
HuPyV	human polyomavirus
IBR	infectious bovine rhinotracheitis
ICANS	immune effector cell-associated neurotoxicity syndrome
ICU	intensive care unit
IFN-γ	interferon-gamma
Ig	immunoglobulin
IL	interleukin
IMWG	International Myeloma Working Group
IMWG criteria	IMWG response criteria
IRC	Independent Response Committee
ITT	intention-to-treat
LD chemotherapy	lymphodepleting chemotherapy
Legend	Nanjing Legend Biotech, Inc.
LTR	long terminal repeat
K_d	apparent binding affinity
MAS	macrophage activation syndrome
MCB	master cell bank
mDC	myeloid dendritic cells
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
[redacted]	[redacted]
MR	minimal response
MRC-5 cells	human fetal lung fibroblast cells
NCG	NOD-Prkdc^{em26Cd52}Il2rgem26Cd22/Nju
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	not evaluable
[redacted]	[redacted]
OS	overall survival
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PCV	porcine circovirus
PD	progressive disease
PFS	progression free survival
PI3	parainfluenza-3
PMDA	Pharmaceuticals and Medical Devices Agency
PPT	polypurine tract
PPV	porcine parvovirus
PR	partial response

PS	performance status
PT	preferred term
PT-1	porcine testis cells
PVB19	parvovirus B19
qPCR	quantitative polymerase chain reaction
QOL	quality of life
[redacted]	[redacted]
RABV	rabies virus
RCL	replication competent lentivirus
Reo	reo virus
RRE	Rev-responsive element
RSV	respiratory syncytial virus
RUBV	rubella virus
sCR	stringent complete response
SD	stable disease
SIN	self-inactivating
SMQ	standardised MedDRA queries
SOC	system organ class
SPR	surface plasmon resonance
Study MMY2001	Study 68284528MMY2001
Study MMY2003	Study 68284528MMY2003
Study MMY3002	Study 68284528MMY3002
SV40	simian virus 40
$t_{1/2}$	half-life of the transgene level
t_{bql}	time of the first BQL (below quantification limit) transgene level
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)
TTR	time to response
Vero cells	African green monkey kidney epithelial cells
VGPR	very good partial response
VHH	variable fragments of heavy chain antibody
VSV-G	vesicular stomatitis virus G glycoprotein
VZV	varicella zoster virus
WCB	working cell bank
WNV	West Nile virus
WPRE	woodchuck hepatitis virus posttranscriptional regulatory element