March 5, 2021
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Lisocabtagene Maraleucel
Brand Name	Breyanzi Suspension for Intravenous Infusion
Applicant	Celgene Corporation
Date of Application	June 22, 2020 (Application for marketing approval)

Results of Deliberation

In the meeting held on February 17, 2021, the Committee on Regenerative Medicine Products and Biotechnology made the following decision and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The approval is not classified as a conditional and time-limited approval. 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 at medical institutions well-equipped for handling emergencies and prepared for appropriate measures including the management of cytokine release syndrome, under the supervision of a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation.
2. Because only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product in the post-marketing setting, until data from a certain number of cases are collected, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data, and thereby to take necessary measures to ensure the proper use of the product.

Review Report

February 2, 2021
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Breyanzi Suspension for Intravenous Infusion
Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Lisocabtagene Maraleucel
Applicant	Celgene Corporation
Date of Application	June 22, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous CD4-positive T cells and CD8-positive T cells isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets CD19 antigen is introduced by using a recombinant lentiviral vector.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 7 of 2018 [*30 sai*]; PSEHB/MDED Notification No. 1001-1 dated October 1, 2018, 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 a certain level of efficacy in the treatment of relapsed or refractory large B-cell lymphoma and relapsed or refractory follicular lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications or performance as well as dosage and administration or method of use shown below, with the following approval conditions.

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed indolent non-Hodgkin lymphoma, high-grade B-cell lymphoma

Relapsed or refractory follicular lymphoma

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen who are ineligible for autologous hematopoietic stem-cell transplantation or have a history of relapse after autologous hematopoietic stem-cell transplantation, and meet any of the following criteria:

- Patients with large B-cell lymphoma other than transformed indolent non-Hodgkin lymphoma and patients with follicular lymphoma: ≥2 lines of prior chemotherapy in first-onset patients or ≥1 line of prior post-relapse chemotherapy in relapsed patients, which failed to achieve complete response or resulted in another relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from follicular lymphoma: a total of ≥2 lines of prior chemotherapy including ≥1 after transformation, which failed to achieve complete response or resulted in relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from indolent B-cell non-Hodgkin lymphoma other than follicular lymphoma: ≥2 lines of prior chemotherapy after transformation, which failed to achieve complete response or resulted in relapse

Dosage and Administration or Method of Use

Leukapheresis at the medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis product
   The leukapheresis product collected is packed in a refrigerated container set at 1°C to 10°C and transported to the manufacturing site of Breyanzi.

Receipt of Breyanzi at the medical institution and administration

3. Receipt and storage of Breyanzi
   Frozen Breyanzi is accepted and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before infusion
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 2 to 7 days prior to Breyanzi infusion:
   Fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days, and cyclophosphamide (anhydrate) 300 mg/m^2 is infused intravenously once daily for 3 days. The

doses may be reduced depending on the patient's condition (e.g., renal impairment).

5. Infusion of Breyanzi

   Breyanzi is thawed immediately before infusion. The usual adult dosage is a total of 100×10^6 (range, 44×10^6-100×10^6 cells) of CAR-positive viable T cells consisting of CD8-positive cells (20×10^6-50×10^6 cells) and CD4-positive cells (20×10^6-50×10^6 cells), irrespective of body weight. CD8-positive cells are first infused, followed by CD4-positive cells so that the CD8-/CD4-positive cell ratio is 1:1 (range, 0.8-1.2). Re-administration of Breyanzi is not allowed.

Approval Conditions

1. The applicant is required to ensure that the product is used at medical institutions well-equipped for handling emergencies and prepared for appropriate measures including the management of cytokine release syndrome, under the supervision of a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation.
2. Because only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients treated with the product in the post-marketing setting, until data from a certain number of cases are collected, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data, and thereby to take necessary measures to ensure the proper use of the product.

Attachment

Review Report (1)

December 14, 2020

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	Breyanzi Suspension for Intravenous Infusion
Classification	Human cellular/tissue-based products 1. Human somatic cell processed product
Non-proprietary Name	Lisocabtagene Maraleucel
Applicant	Celgene Corporation
Date of Application	June 22, 2020

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product prepared from autologous CD4-positive T cells and CD8-positive T cells isolated from the leukocyte apheresis product of the patient, to which a transgene encoding chimeric antigen receptor (CAR) that targets CD19 antigen is introduced by using a recombinant lentiviral vector.

Proposed Indication or Performance

Relapsed or refractory large B-cell lymphoma

Proposed Dosage and Administration or Method of Use

Leukapheresis at a medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected.
2. Transportation of leukapheresis product
   The leukapheresis product is packed and transported under refrigerated conditions to the manufacturing site of Breyanzi.

Receipt of Breyanzi at the medical institution and administration

3. Receipt and keeping of Breyanzi
   Frozen Breyanzi is accepted and cryopreserved until immediately before use.
4. Treatment before infusion
   Lymphodepleting chemotherapy.
   1) Fludarabine phosphate 30 mg/m^2 and cyclophosphamide (anhydrate) 300 mg/$m^2$are infused

intravenously once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).

2) Breyanzi is infused 2 to 7 days after the completion of lymphodepleting chemotherapy.

5. Infusion of Breyanzi

Breyanzi is thawed immediately before infusion. The usual adult dosage is 100×10^6 (irrespective of body weight) CAR-positive viable T cells (CD8-positive and CD4-positive cell components) intravenously infused as a single dose. Refer to the shipping certificate for the actual cell count and dose.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Breyanzi comprises cultured autologous peripheral cluster of differentiation (CD) 4-positive and CD8-positive T cells transduced with recombinant lentiviral vector containing a chimeric antigen receptor (CAR) that specifically recognizes CD19. Breyanzi is a regenerative medical product to be infused intravenously with an expected therapeutic effect by its pharmacological action like pharmaceutical products.

The Breyanzi CAR consists of a murine single-chain variable fragment (scFv) specifically recognizing CD19, a human immunoglobulin (Ig) G4 hinge domain, a human CD28 transmembrane domain, and human 4-1BB and CD3-ζ intracellular signaling domains. Breyanzi contains, in addition to CAR, a cell surface marker "truncated epidermal growth factor receptor (EGFRt*)" transduced to evaluate transduction rates. When recognizing CD19-expressing cells, Breyanzi induces the activation and proliferation of these genetically modified T cells, thereby obtaining effector functions such as a cytopathic effect. Through these actions, Breyanzi is expected to kill CD19-positive B-cell tumor cells.

Breyanzi was designated as an orphan regenerative medical product with the intended indication or performance for treatment of "aggressive B-cell non-Hodgkin lymphoma" on October 1, 2018 (Orphan Regenerative Medical Product Designation No. 7 of 2018 [*30 sai*]).

1.2 Development history etc.

Malignant lymphoma is a malignant tumor of transformed mature lymphocytes, a type of blood cells derived from hematopoietic stem cells. Tumor cells proliferate in lymphatic tissues (such as lymph nodes) and in extralymphatic organs, forming lesions such as tumor mass. Malignant lymphoma presents with various symptoms depending on the site of the lesion, but with enlarged lymph nodes in the vast majority of patients, accompanied by systemic symptoms such as pyrexia, loss of appetite, and decreased body weight. Histologically, malignant lymphoma is roughly categorized into Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). NHL, classified as either B-cell NHL or T-cell NHL, is dominated by B-cell lymphoma which expresses characteristic pan-B-cell antigen such as CD19 and CD20 on the cell surface. Diffuse large B-cell lymphoma (DLBCL), which accounts for approximately 45% of all patients with malignant lymphoma among B-cell NHL in Japan, is a type of large B-cell lymphoma. DLBCL may occur *de novo* or arise by transformation from indolent NHL such as follicular lymphoma (FL). Large B-cell lymphoma other than DLBCL includes primary mediastinal large B-cell lymphoma (PMBCL), which accounts for 2% to 3% of B-cell NHL. Treatment of relapsed or refractory large B-cell lymphoma varies by tissue type. For DLBCL, high-dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT) are recommended in patients eligible for high-dose chemotherapy. In Japan, no additional chemotherapy is established for patients with ≥2 lines of prior chemotherapy, but tisagenlecleucel (brand name, Kymriah Suspension for Intravenous Infusion), CAR T cells similar to Breyanzi, was approved in March 2019.

* Truncated human epidermal growth factor receptor, a nonfunctional cell surface protein. Whereas EGFR is composed of 4 extracellular domains (I–IV), a transmembrane domain, and an intracellular domain, EGFRt lacks [redacted].

A foreign phase I study (Study 017001) of Breyanzi was conducted in patients with relapsed or refractory B-cell NHL by Juno Therapeutics Inc. (Juno Inc.) from January 2016. Subsequently, a global phase II study (Study JCAR017-BCM-001 [Study BCM-001]) in patients with relapsed or refractory aggressive B-cell NHL was started in June 2018 by the applicant.

In the US, a marketing application (application) for Breyanzi was submitted in December 2019 with the results of Study 017001 as pivotal data. Breyanzi was designated as a Breakthrough Therapy in December 2016.

In Japan, the enrollment in Study BCM-001 started in [redacted] 20[redacted].

Recently, the applicant submitted the approval application for Breyanzi with the results of Studies 017001 and BCM-001 as pivotal data.

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

Breyanzi is prepared from CD4-positive T cells and CD8-positive T cells isolated from the patient's own peripheral blood mononuclear cells (PBMC) via a leukapheresis procedure. The isolated CD4-positive T cells and CD8-positive T cells are transduced with a lentiviral vector containing a transgene encoding CAR directed against human CD19. The transduced T cells are expanded in culture.

2.1 Viral vector

The gene transfer vector is a lentiviral vector that is derived from human immunodeficiency virus (HIV)-1 and has genetically modified self-inactivating long terminal repeat (LTR), which deprives the vector of replication competence. The anti-CD19 chimeric antigen receptor (anti-CD19 CAR) gene transferred by the viral vector includes sequences encoding the scFv region of the anti-CD19 mouse monoclonal antibody (mouse hybridoma cell line FMC63), human IgG4-derived hinge domain, human CD28-derived transmembrane domain, human 4-1BB and human CD3-ζ intracellular signaling domains.

The viral vector genome is composed of HIV-1-derived LTR, packaging signal (Ψ), [redacted] and [redacted] and anti-CD19 CAR transgene, EGFRt-coding sequence, and N-terminal signal peptide sequence of α-chain of human granulocyte-macrophage colony-stimulating factor receptor inserted into [redacted]. Most of the HIV-1 genome is deleted. Components required for the production of the viral vector were divided into 3 plasmid vectors (i.e., Gag/Pol, Rev, and glycoprotein of the vesicular stomatitis virus [VSV-G]), in order to minimize homologous recombination and thereby to prevent the emergence of a replication competent lentivirus (RCL).

2.1.1 Plasmids

The viral vector is generated from the transfer plasmid and 3 helper plasmids. Each plasmid contains either anti-CD19 CAR, Gag/Pol, Rev, or VSV-G, respectively under the control of [redacted] or [redacted]. The control items of the plasmids include [redacted], [redacted], [redacted], [redacted], bacterial endotoxin, [redacted],

[redacted], [redacted], [redacted], sterility, mycoplasma, and [redacted].

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

The viral vector is produced using human embryonic kidney 293T/17 (HEK293T/17 cells). HEK293T/17 cells ([redacted]; [redacted]) obtained from the American Type Culture Collection (ATCC) were used to generate master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and end of production cells (EOP) were subjected to characterization and purity tests in accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines. Table 1 shows tests performed for adventitious agents. The results demonstrated the genetic stability throughout the manufacturing period, and neither viral nor non-viral adventitious agents were detected by any of the tests.

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

Table 1. Tests for adventitious agents

In vitro virus tests (MRC-5 cells, Vero cells, and HeLa cells)
In vivo virus tests (suckling mice, mature mice, and embryonated hen's eggs)
Bovine virus tests (BAV, BTV, BRSV, BPV, BVDV, PI3, IBRV, REO3, and RABV)
Porcine virus tests (PPV, TGEV, PAV, BVDV, RABV, REO3, and HEV)
Bovine polyoma virus test
Human virus tests (HSV-1/2, PVB19, EBV, SV40, HHV5 (CMV), HHV6, HHV7, HHV8, HBV, HIV-1, HIV-2, HTLV-1/2, HCV, and HAV)
Reverse transcriptase activity test
Electron microscopy
Sterility
Mycoplasma test
Bacterial endotoxin test

2.1.3 Manufacturing process of viral vector

The manufacturing process of the viral vector consists of cultivation of WCB, transformation/[redacted], harvest of viral vector, clarification/[redacted]/concentration, adjustment/[redacted], [redacted], filling, freezing/storage, and testing.

Critical steps include [redacted].

Process validation of the viral vector manufacturing process was implemented on a commercial-product scale.

2.1.4 Safety evaluation of adventitious agents in the viral vector

Table 2 shows raw materials of biological origin other than HEK293T/17 cells used in the manufacturing process of the viral vector, all of which meet the Standards for Biological Ingredients

Table 2. Raw materials of biological origin other than HEK293T/17 cells

Raw material name	Animal	Site	Process
FBS (a)	Cattle	Blood	[redacted]
FBS (b)	Cattle	Blood	[redacted]
Bovine serum	Cattle	Blood	[redacted]
FBS (c)	Cattle	Blood	[redacted]
Bovine milk protein	Cattle	Milk	[redacted]

[redacted] or [redacted] after the viral vector production is tested for adventitious viruses, mycoplasmas, [redacted], and RCL for each batch, as shown in Section 2.1.7. Also, a sterility test and RCL test are performed on [redacted].

The above tests are proposed as specification tests for the viral vector.

2.1.5 Manufacturing process development of viral vector

Tables 3 and 4 show the main changes in the development process of the viral vector.

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

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

Table 3. Changes of manufacturing process of viral vector

Manufacturing process	Change, etc.
From Process A to Process B	Changes in [redacted]
From Process B to Process C	Changes in [redacted]

Table 4. Viral vector manufacturing process employed in the manufacture of the product used in each non-clinical and clinical study

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

2.1.6 Characterization of viral vector

2.1.6.1 Structure and characterization

Characterization performed is shown in Table 5.

Table 5. Characterization items

Tests on viral vector	Viral vector structure (morphology, particle size, nucleic acid element), expression of structural protein and enzyme proteins ([redacted] protein, reverse transcriptase, integrase, protease, and VSV-G protein), [redacted] titer ([redacted] within transduced cells), ratio of infectious particles to all particles, [redacted], impurities (host cell DNA, host cell protein, plasmid DNA, residual Impurity A, residual BSA)
Characterization of component cells of Breyanzi genetically modified by viral vector	Vector copy number, CAR expression rate, IFN-γ-producing capacity, gene insertion site analysis of viral vector [see Section 4.2.1]

2.1.6.2 Process-related impurities

RCL, host cell DNA, host cell protein, plasmid DNA, Impurity A, bovine serum albumin (BSA),

Impurity B, Impurity C, and Impurity D were identified as process-related impurities. All process-related impurities except for RCL and Impurity D were demonstrated to be adequately removed by the manufacturing process. RCL is controlled by performing the test on EOP and bulk viral vector, and Impurity D by the test on viral vector solution.

2.1.7 Control of viral vector

The proposed specifications for the viral vector include description, identification (method), pH, purity (host cell DNA, plasmid DNA, and host cell protein), bacterial endotoxins, sterility (and), mycoplasma ( ), virus tests (adventitious virus tests on [, *in vitro* virus tests (human fetal lung fibroblasts [MRC-5 cells], African green monkey kidney epithelial cells [Vero cells], and HEK293 cells), and bovine virus tests (cytopathic effect [CPE] and haemadsorption [HAD] [and cells], and immunofluorescent staining [, , , , , and])]), RCL (method) (and), titer (in transduced cells against and), and titer (of transduced cells).

2.1.8 Stability of viral vector

Table 6 shows a summary of major stability studies for the viral vector.

Table 6. Summary of major stability studies for the viral vector

Study	Manufacturing process	Number of batches	Storage condition	Study period	Storage form
Long-term testing	Proposed process	3	−70°C to −90°C	months[*1]	Bromobutyl rubber stopper and vial
Stress-testing	Proposed process[*2]	2	°C °C °C °C		

*1
*2

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

The stress testing evaluated and , neither of which showed any significant changes throughout the study period at °C and °C, whereas at °C, a decrease of was found at .

Based on the above, a shelf life of months was proposed for the viral vector when stored in a vial sealed with a bromobutyl rubber stopper at °C.

2.2 Product

2.2.1 Description and composition of product and formulation development

The product is a set of CD8-positive T cell vials (5 mL) and CD4-positive T cell vials (5 mL), each containing ≥1.1×10^6 anti-CD19 CAR T cells, allowing infusion of 44×10^6 to 100×10^6 viable CD19 CAR T cells (CD8-positive/CD4-positive T cell ratio, 0.8-1.2). Excipients contained in the product include CryoStor CS10, composite electrolytes, and human serum albumin.

2.2.2 Manufacturing process

The manufacturing process of the cells serving as a component of the product (component cells) and product includes washing of leukapheresis material, [redacted], manufacture of CD8-positive T cell vials ([redacted]/labeling/filling/freezing/storage/testing/packaging), and manufacture of CD4-positive T cell vials ([redacted]/labeling/filling/freezing/storage/testing/packaging), and packaging.

Critical steps include [redacted].

Process validation was conducted on the manufacturing process of the component cells and the product on a commercial-production scale.

2.2.3 Safety evaluation of adventitious agents

2.2.3.1 Patient's peripheral blood mononuclear cells

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

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

Table 7 shows raw materials of biological origin, etc., used in the manufacturing process. All of these raw materials were confirmed to conform to the Standard for Biological Ingredients.

Table 7. Raw materials of biological origin, etc., other than patient's peripheral blood mononuclear cells used in the manufacturing process

Raw material name	Animal	Origin or material	Process
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Anti-[redacted] antibody	Mouse	Hybridoma cells	[redacted]
Human serum albumin (a)	Human	Blood	[redacted]
Human serum albumin (b)	Human	Blood	[redacted]
FBS	Cattle	Blood	[redacted]

2.2.4 Manufacturing process development

Table 8 shows the main changes in the development process of the component cells and product. Table 9 shows manufacturing processes of the component cells used in nonclinical and clinical studies. The component cells manufactured by Process v4 are used for the commercial product.

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

The manufacturing process development employs the QbD concept.

Table 8. Changes of manufacturing process of component cells

Manufacturing process	Main changes, etc.
From Process v1 to Process v2	Changes of [redacted] and [redacted]
From Process v2 to Process v3	Changes of [redacted], [redacted], and [redacted]
From Process v3 to Process v4	Changes of [redacted], [redacted], and [redacted], and addition of [redacted]

Table 9. Manufacturing process of component cells used in nonclinical and clinical studies

Manufacturing process	Nonclinical or clinical studies
Process v1	Non-clinical studies, Study 017001
Process v2	Non-clinical studies, Study 017001
Process v3	Non-clinical studies, Study 017001
Process v4 (proposed process)	Non-clinical studies, Studies 017001 and BCM-001

2.2.5 Characterization

2.2.5.1 Structure and characterization

Characterization was performed as shown in Table 10.

Table 10. Characterization of component cells

Structure and physicochemical properties	Structure of anti-CD19 CAR (amino acid sequence, structure/size, [redacted]), transduction rate, vector copy number, number of CAR expressed per cell, immunophenotype ([redacted], T cells [CD3-positive cells, CD4-positive cells, CD8-positive cells], [redacted], [redacted], [redacted], [redacted], [redacted]), T-cell subset analysis ([redacted], [redacted], [redacted], [redacted], [redacted]), [redacted], gene insertion site analysis of viral vector [see Section 4.2.1], and EGFRt expression
Biological properties	CD19-binding activity, release of IFN-γ in response to CD19 antigen specific stimulation, cell proliferation in response to CD19 antigen-specific stimulation, analysis of T cell function-related cytokines, and CD19 antigen specific cytotoxic activity
Purity	Cell viability, non-target cells ([redacted], [redacted], [redacted], [redacted], [redacted]), red blood cells, platelets, residual viral vector, [redacted] protein, host cell DNA, host cell protein, plasmid DNA, BSA, Impurities A, E, F, G, H, I, J, K, L, M, N, O, P, Q, and R

2.2.5.2 Process-related impurities

Process-related impurities include residual viral vector, [redacted] protein, host cell DNA, host cell protein, plasmid DNA, BSA, Impurities A, E, F, G, H, I, J, K, L, M, N, O, P, Q, and R.

Impurity G is controlled by the specifications of the product. Other process-related impurities were confirmed to be adequately removed during the manufacturing process.

Residual viral vector was subjected to process evaluation for Process v4, and the amount in the final

product has been demonstrated to be below the lower limit of quantitation (/mL).

2.2.6 Control of product

The proposed specification for CD8-positive T cell vials and for CD4-positive T cell vials includes description, identification (method), purity (cell viability rate, copy number of vector, and residual bead count), bacterial endotoxins, mycoplasma, sterility, percentage of CD3-positive cells, percentage of CD4-positive cells (only for CD4-positive T cell vials), percentage of CD8-positive cell (only for CD8-positive T cell vials), biological activity (interferon-gamma [IFN-γ] production), and content (number of anti-CD19 CAR T cells [viable cells]). The sum of the content in each vial is included in the specification for the product comprising CD8-positive T cell and CD4-positive T cell vials.

2.2.7 Stability of product

Table 11 shows a summary of major stability studies for the product.

Table 11. Summary of major stability studies for the product

Study	Number of batches	Manufacturing process	Origin	Storage condition	Study period	Storage form	Vial volume
Long-term testing	3	Proposed process	Healthy adults	≤−130°C	12 months[*1]	Cyclic olefin copolymer vial	5 mL
	1	Proposed process[*2]	Patients		months[*3]		
Stress testing	2	Proposed process[*2]	Healthy adults				
	4		Patients				
In-use stability testing	2	Proposed process[*2]	Healthy adults	15°C-25°C			

*1 The stability study is ongoing up to 24 months.
*2 Manufactured at .
*3 The stability study is ongoing up to 18 months.

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

The stress testing evaluated , , , and , which showed decreased and decreased . A decrease in and was observed on storage .

The in-use stability testing evaluated , , , , , , , , and . Throughout the study period, no clear change was observed in the quality attributes.

Based on the above, a shelf life of 12 months has been proposed for the product when stored in cyclic olefin copolymer vials at ≤−130°C. Administration should be completed within 2 hours at room temperature after thawing.

2.3 QbD

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

- Identification of critical quality attributes (CQAs)

  Based on the information obtained through the development of the product and related knowledge, etc., the following CQAs were identified regarding process-related impurities and product characteristics:

  - CQAs of viral vector

    [redacted], bacterial endotoxin, mycoplasmas, sterility, RCL, adventitious viruses, and transmissible spongiform encephalopathy (TSE)

  - CQAs of CD8-positive T cell vials, CD4-positive T cell vials, and product

    [redacted], mycoplasma, sterility, and bacterial endotoxin

- Process characterization

  Process parameters were classified and characterization of each process was performed by risk assessment based on their effect on CQA.

- Establishment of control method

  Based on the knowledge on the process including those obtained from the above process characterization, the method for controlling the quality attributes of the product was established by the combination of process parameter control, in-process control, and specifications [see Section 2.2.5.2 for the control of process-related impurities].

2.R Outline of the review conducted by PMDA

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

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

The applicant submitted the following data relating to the primary pharmacodynamics or performance of Breyanzi: *In vitro* studies, *in vivo* studies, and secondary pharmacology studies.

3.1 *In vitro* studies

3.1.1 Binding characteristics of FMC63 scFv (CTD 4.2.1.1.1)

The binding characteristics of single-chain variable region derived from anti-CD19 murine monoclonal antibody (mouse hybridoma strain FMC63) (FMC63 scFv), the CD19-binding site of CAR of Breyanzi, was investigated. The following results were obtained:

- Binding activity of FMC63 scFv to CD19 forced expressing human chronic myeloid leukemia (K562 cells) was evaluated by kinetic exclusion assay. The binding affinity (Kd) of FMC63 scFv to CD19 was estimated to be 0.9 nmol/L.

- The equilibrium dissociation constant of FMC63 scFv to human CD19 was estimated to be 21 nmol/L by surface plasmon resonance
- Epitope analysis by Pepscan showed that FMC63 scFv bound to 2 noncontiguous sequences of human CD19 (residues 113VNVEGSGELFR123 and 129LGGLGCGLKNR139).

3.1.2 *In vitro* evaluation of CAR end-domain activity of Breyanzi (CTD 4.2.1.1.2)

In order to evaluate the role of the intracellular signal domain in CAR signal transduction, 4 types (nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB], nuclear hormone receptor-77 [Nur77], nuclear factor of activated T-cells [NFAT], and activator protein [AP]-1) of Jurkat T cell reporter strains[1)] were engineered to express normally functioning CAR or CAR with mutated CD3ζ or 4-1BB, and co-cultured with K562 cells expressing human CD19 or B-cell maturation antigen (BCMA), and TdTomato fluorescence was measured.

When Jurkat T cell reporter strain transduced with normally functioning CAR was co-cultured with CD19-expressing K562 cells, TdTomato fluorescence was detected in all CAR-expressing Jurkat T cell reporter strains. In contrast, when Jurkat T cell reporter strain transduced with CAR with mutated CD3ζ was co-cultured with CD19-expressing K562 cells, TdTomato fluorescence was observed in NF-κB reporter strain, albeit weaker than in the strain with normal CAR, whereas no TdTomato fluorescence was observed with the other 3 types of reporter strains. When Jurkat T cell reporter strain with CAR with mutated 4-1BB was co-cultured with CD19-expressing K562 cells, TdTomato fluorescence was observed in Nur77, NFAT, and AP-1 reporter strains, while the fluorescence was weaker in NF-κB reporter strain than in cells expressing normal CAR. When co-cultured with BCMA-expressing K562 cells, none of CAR-expressing Jurkat T cell reporter strains showed TdTomato fluorescence.

3.1.3 Breyanzi activation by CD19-expressing cells (CTD 4.2.1.1.3)

Breyanzi manufactured from T cells of 2 healthy persons or pseudo-transduced cells (non-CAR-expressing cultured T cells derived from either 1 of the persons) were co-cultured with 5 types (Daudi, Raji, Nalm-6, Granta-519, and JeKo-1)[2)] of CD19-expressing human target cell lines, and the amount of cytokines (IFN-γ, interleukin [IL]-2, and tumor necrosis factor [TNF]α) in the culture supernatant and CD25 and CD69 expression were evaluated. When Breyanzi was co-cultured with the 5-types of CD19-expressing human target cell lines, the amount of the cytokines in the culture supernatant and the percentage of CD25-and CD69-expressing T cells increased in all combinations. In contrast, when pseudo-transduced cells were co-cultured with the 5-types of CD19-expressing human target cell lines, no change was observed in the amount of the cytokines in the culture supernatant.

3.1.4 Effect on FL and PMBCL strains (CTD 4.2.1.1.4 and CTD 4.2.1.1.5)

Breyanzi was manufactured from T cells of a healthy person, and pseudo-transduced cells

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1) A cell line engineered to express an alternative red fluorescent protein to detect Nur77, NFAT, AP-1, or NF-κB activation. Jurkat T cell line was genetically engineered to express TdTomato fluorescence in correlation with NFAT, AP-1, or NF-κB responsive promoter element or with Nur77 promoter to allow confirmation of whether T cell activation signal is induced by the binding of CAR of JCAR017 cells to CD19.

2) CD19 expression density in the target cell line was within the range from 31,657 to 806,265/cell.

(non-CAR-expressing T cells derived from the person) were co-cultured (16-18 hours) with a cell line derived from a patient with FL or a patient with PMBCL to evaluate the amount of cytokines (IFN-γ, IL-2, and TNFα) in the culture supernatant and CD25 and CD69 expression. Co-culture of Breyanzi with the cell line derived from a patient with FL or PMBCL resulted in increased amount of the cytokines in the culture supernatant and percentage of T cells expressing CD25 and CD69. Comparison of the viability of each cell line co-cultured (16-18 hours) with Breyanzi or with the pseudo-transduced cells showed decreased viability of the cell line derived from the patient with FL or PMBCL co-cultured with Breyanzi.

3.1.5 *In vitro* cytotoxic activity of Breyanzi derived from patients (CTD 4.2.1.1.6)

Breyanzi derived from 2 patients with NHL was co-cultured (6 days) with CD19-positive K562 cells or CD19-negative K562 cells, and the cytotoxic activity of Breyanzi was evaluated by the decrease/increase of K562 cell count. The CD19-negative K562 cell count increased by ≥15 fold by co-culture with Breyanzi, whereas the CD19-positive K562 cell count decreased to 14% to 32% of the original level by co-culture with Breyanzi.

3.1.6 Proliferative response of Breyanzi derived from patients with NHL to 6-day stimulation of CAR (CTD 4.2.1.1.7, CTD 4.2.1.1.8, CTD 4.2.1.1.9, and CTD 4.2.1.1.10[3)])

CD8-positive T cells and CD4-positive T cells contained in Breyanzi derived from patients with NHL were cultured (6 days) in isolation (2×10^4 cells each) or in combination at the CD8-positive T cell/CD4-positive T cell ratio of 1:1 (1×10^4 each of CD8-positive and CD4-positive T cells, 2×10^4 cells in total), and growth of CD8-positive T cells and CD4-positive T cells under continuous stimulation[4)] of CAR was measured using Nexcelom Celigo High Throughput Micro-Well Image Cytometer. When cultured in isolation, the count of CD8-positive T cells and CD4-positive T cells increased by 4- to 5.9-fold and by 3.1- to 13.3-fold, respectively. When co-cultured at the CD8-positive T cell/CD4-positive T cell ratio of 1:1, the cell count increased by 6.2- to 16.5-fold.

3.2 *In vivo* studies

3.2.1 *In vivo* primary pharmacodynamics (CTD 4.2.1.1.11)

Using immunodeficient mice transplanted with human CD19-positive B-cell lymphoma cells (Raji cells) (mouse model of lymphoma), the antitumor effect of Breyanzi against human CD19-positive B cell lymphoma cells was evaluated. The day of the transplantation of human CD19-positive B cell lymphoma cells to mice was taken as the day of the study start (Day 0). On Day 7, Breyanzi at 3 dose levels (low dose group, 1.25×10^5 cells/animal; medium dose group, 5×10^5 cells/animal; high dose group, 2×10^6 cells/animal) was administered intravenously, and in the control group, the negative control product (non-transduced product, 2×10^6 cells) was administered intravenously. The body weight, tumor mass, and viability of the mice were investigated up to Day 100. The body weight decreased by 15% to 30% from baseline in the control mice group and in the low dose group. In the medium and high dose groups in contrast, the body weight was maintained, and decreased tumor mass and prolonged survival were observed as compared with other groups.

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3) CTD 4.2.1.1.8, 4.3.1.1.9, and 4.2.1.1.10 are reference data.

4) CAR was stimulated by anti-idiotype antibody specific to the extracellular domain of CAR of Breyanzi.

3.3 Secondary pharmacodynamics

3.3.1 Comparison of CD19 amino acid sequence among humans, non-human primates, and mice (CTD 4.2.1.2.1[5])

The similarity in CD19 amino acid sequences among humans, 2 types of non-human primates (NHPs) (rhesus monkeys and cynomolgus monkeys), and mice was evaluated by multiple sequence alignment using Clustal omega algorithm.

CD19 amino acid sequences of humans and mice were 67% identical over the entire sequence and 58% identical in the extracellular domain. The sequences of 2 NHPs were 100% identical with each other, 92% identical to the entire human sequence and 88% identical to the human extracellular domain. Also, it was confirmed that the amino acid sequence of human CD19 epitope to which FMC63 scFv binds is different from that of rhesus monkeys and mice at multiple sites.

3.3.2 Inter-species cross-reactivity of Breyanzi (CTD 4.2.1.2.2)

Breyanzi was co-cultured with fluorescence-labeled human-, NHP-, and mice-derived CD19-expressing cells (Raji cells, Cyno B cells, and A20 cells), and the cytotoxic activity of Breyanzi was evaluated using a fluorescent plate reader. The cytotoxic activity was observed against human-derived CD19-expressing cells but not against NHP-derived CD19-expressing cells or mouse-derived CD19-expressing cells.

The binding activity of FMC63 scFv to human-, NHP-, and mouse-derived CD19-expressing cells was investigated by flow cytometry. FMC63 scFv bound to human-derived CD19-expressing cells but not to NHP- or mouse-derived CD19-expressing cells.

3.3.3 Evaluation of binding profile of FMC63 scFv-Fc using human membrane protein-expressing cells (CTD 4.2.1.2.3[6])

Using immobilized human HEK cells expressing fusion protein of FMC63 scFv and Fc (FMC63 scFv-Fc) and 4,417 types of human proteins separately, binding of Breyanzi to cell membrane proteins other than CD19 was investigated.

CD19 and phosphorylase kinase regulatory subunit beta were identified as proteins that specifically bind to FMC63 scFv-Fc. However, phosphorylase kinase regulatory subunit beta is not considered to have an extracellular domain, and the applicant thus considers that FMC63 scFv-Fc is unlikely to bind to phosphorylase kinase regulatory subunit beta *in vivo*.

3.R Outline of the review conducted by PMDA

3.R.1 Efficacy of Breyanzi

The applicant's explanation about the efficacy of Breyanzi:

In *in vitro* studies, Breyanzi secreted cytokines such as IFN-γ in a CD19 antigen-dependent manner and exhibited proliferative capacity. Also, Breyanzi showed cytotoxicity specific to CD19-expressing

5) Data in CTD 4.2.1.2.1 are reference data.
6) Data in CTD 4.2.1.2.3 are reference data.

cells.

In *in vivo* studies, the administration of Breyanzi to a mouse model of lymphoma decreased tumor mass and prolonged survival while maintaining the body weight.

Secondary pharmacology studies showed that Breyanzi binds to human CD19 but not to mouse or NHP CD19.

The above results suggest that Breyanzi recognizes B-cell malignant lymphoma cells in a CD19-dependent manner, thereby exhibiting cytotoxic activity.

PMDA accepted the explanation of the applicant.

3.R.2 Interactions between Breyanzi and drugs with EGFR-inhibitory effect

PMDA asked the applicant to explain about the possibility that drugs with an EGFR-inhibitory effect, such as anti-EGFR antibody, selectively deplete Breyanzi because EGFRt is expressed on the cell surface of Breyanzi.

The applicant's explanation:
Breyanzi was administered intravenously to a mouse model of lymphoma, followed by cetuximab (genetical recombination) (cetuximab), an anti-EGFR antibody, and Breyanzi in the peripheral blood and the spleen was measured using flow cytometry. Breyanzi was not detected either in the bone marrow or peripheral blood. Animals in the cetuximab group showed increased tumor volume presumably due to the depletion of Breyanzi, and decreased viability. These results suggest that anti-EGFR antibody drugs cause the depletion of Breyanzi in bone marrow, peripheral blood, and spleen.

The "Interactions" section of the package insert will present cautionary advice on the administration of anti-EGFR antibody after Breyanzi infusion.

PMDA accepted the explanation of the applicant.

4. Data Relating to Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the following data relating to non-clinical safety of Breyanzi: The results from pharmacology studies of Breyanzi in a mouse model of lymphoma, gene insertion site analysis of the lentiviral vector, analysis of IL-2-dependent *in vitro* cell growth, human tissue cross-reactivity studies on FMC63 scFv, and safety evaluation of impurities and excipients.

4.1 General toxicity

Breyanzi is a CAR T cell product manufactured from human T cells. The administration of Breyanzi to animals causes graft-versus-host disease. In addition, CAR of Breyanzi is a mouse-derived scFv that specifically recognizes human CD19 and does not bind to CD19 of experimental animals [see Section 3.3.2]. For these reasons, considering adequate safety evaluation of Breyanzi in experimental animals

infeasible, *in vivo* toxicity studies were not conducted.

4.1.1 Study in mouse model of lymphoma treated with Breyanzi (CTD 4.2.1.1.11)

In the study administering a single intravenous dose of Breyanzi up to 2×10^6 cells to a mouse model of lymphoma [see Section 3.2.1], body weight and viability were evaluated. No toxicity caused by Breyanzi was observed.

4.2 Evaluation of the possibilities of tumorigenesis and malignant transformation

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

4.2.1 Gene insertion site analysis of lentiviral vector (CTD 4.2.3.3.1.1)

The gene insertion site was confirmed by a next-generation sequencer analysis (Table 12). Results did not suggest any increase in the effect on proto-oncogene, gene insertion sites common to cancers, or regions related to growth regulation. Based on the above results, the applicant explained that the vector gene insertion poses only a low risk of malignant transformation of Breyanzi.

Table 12. Gene insertion site analysis of lentiviral vector

Test system and study method	Results
The gene insertion site was identified by the analysis of genomic DNA extracted from Breyanzi using a next-generation sequencer.	• The same insertion pattern as that of wild-type lentivirus (insertion into a region containing activating chromatin mark, active transcription region, and a region with high GC content) was observed. • Selective insertion into proto-oncogenes, common cancer-related genes, or genes related to growth regulation was not observed.

4.2.2 *In vitro* analysis of IL-2-dependent cell growth (CTD 4.2.3.4.3.1)

An *in vitro* growth study on Breyanzi in the presence or absence of IL-2 (Table 13) did not show IL-2-independent cell growth.

Table 13. *In vitro* analysis of IL-2-dependent growth of Breyanzi

Test system and study method	Results
Breyanzi was cultured in the presence or absence of IL-2, and cell viability was evaluated up to Day 61.	In the presence of IL-2, the cell viability showed a consistent decrease from Day 9 of culture. In the absence of IL-2, in contrast, the cell viability rapidly decreased.

4.3 Human tissue cross-reactivity of FMC63 scFv (CTD 4.2.3.7.7.1)

A cross-reactivity study of FMC63 scFv was conducted using a human tissue panel. A stained image was observed in mononuclear cells in lymphatic tissues, urinary bladder, kidney, urinary duct, and endometrial membrane, which are consistent with the known expression sites of CD19. Although a stained image was also observed in hepatocytes, esophageal epithelial cells, tonsillar epithelial cells, cervical epithelial cells, thymus, and salivary gland, CD19 expression was not reported in these tissues and the study on the binding profile of FMC63 scFv-Fc using cells expressing human cell membrane proteins did not identify any significant target other than CD19 [see Section 3.3.3]. Therefore, the applicant explained that the stained image in these tissues is unlikely to be of any toxicological significance.

4.4 Safety evaluation of impurities

Process-related impurities potentially present in the final product include residual viral vector, [redacted] protein, host cell DNA, host cell protein, plasmid DNA, BSA, Impurities A, E, F, G, H, I, J, K, L, M, N, O, P, Q, and R.

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

4.5 Safety evaluation of excipients

The excipients of Breyanzi are composite electrolyte solution, CryoStor CS10, and human serum albumin. The applicant conducted the safety evaluation of these excipients based on their content levels in Breyanzi at the clinical dose, and considered that they would raise no safety concerns.

4.R Outline of the review conducted by PMDA

Based on the data submitted and the following investigations, PMDA has concluded that Breyanzi raises no particular concerns about the non-clinical safety.

4.R.1 Reproductive and developmental toxicity

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

The applicant's explanation:

Maternal T cells are detected in offspring (*Lab Invest*. 2006;86:1185-92), suggesting a possibility that Breyanzi passes through the placenta into fetal blood and causes B-cell hypoplasia in theory. However, the effect of Breyanzi on fetuses and neonates is unclear at present. In addition, cyclophosphamide hydrate (cyclophosphamide) and fludarabine phosphate (fludarabine) used in lymphodepleting chemotherapy (LD chemotherapy) before Breyanzi infusion are known to have a risk of developmental toxicities such as congenital anomaly in fetuses. Given these, women of childbearing potential will be advised in the package insert to take contraceptive measures for a certain period of time during and after treatment with Breyanzi. The most update report on the clinical safety of Breyanzi (data cut off on [redacted], 20[redacted]) did not report any case of pregnancy after Breyanzi infusion or the administration of Breyanzi during pregnancy.

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

5. Data Relating to Biological Disposition and Outline of the Review Conducted by PMDA

The biological disposition of Breyanzi was investigated based on the information obtained from the non-clinical studies [see Section 3.2.1], and Studies 017001 and BCM-001.

5.1 Non-clinical biological disposition (CTD 4.2.2.1.1)

Following a single intravenous infusion of Breyanzi at 3 dose levels to a mouse model of lymphoma, the CAR-expressing T cell count in the peripheral blood was measured by flow cytometry [see Section 3.2.1].

The CAR-expressing T cell count in the peripheral blood peaked on Day 14 in the low and medium dose groups and on Day 8 in the high dose group, then decreased in all groups.

5.2 Biological disposition

5.2.1 Study 017001 (CTD 5.3.5.2-1 and 5.3.5.2-2)

Change over-time in the level of Breyanzi-derived gene in the peripheral blood was investigated in 238 patients with DLBCL in Study 017001. The dosage regimens of Breyanzi in Study 017001 were as follows. The level of Breyanzi-derived gene was measured by quantitative polymerase chain reaction (qPCR) (detection limit, 5 copies/reaction) using peripheral blood samples collected at baseline and 1, 4, 8, 11, 15, 22, 29, 60, 90, 180, 270, 365, 545, and 730 days after Breyanzi infusion. Also, C_{max}, AUC_{0-28}, and t_{max} of Breyanzi was calculated for patients from whom peripheral blood Breyanzi-derived gene was detected 29 days after infusion or later.

- Dose level 1: 50×10^6 anti-CD19 CAR T cells (25×10^6 CD8-positive T cells, 25×10^6 CD4-positive T cells) (single dose, DL1S; double doses,[7] DL1D)
- Dose level 2: 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells) (single dose, DL2S)
- Dose level 3: 150×10^6 anti-CD19 CAR T cells (75×10^6 CD8-positive T cells, 75×10^6 CD4-positive T cells) (single dose, DL3S)

Figure 1 shows the change over time in the level of Breyanzi-derived gene in the peripheral blood, and Table 14 shows the median values of the parameters of biological disposition, calculated by the level of Breyanzi-derived gene in the peripheral blood. Following the single dose of Breyanzi, the level of Breyanzi-derived gene in the peripheral blood increased and then decreased in a biphasic manner. C_{max} and AUC_{0-28} of Breyanzi-derived gene level in the peripheral blood were similar irrespective of dose level. In 6 patients receiving 2 doses of Breyanzi (DL1D), C_{max} and AUC_{0-28} after the second dose did not significantly increase from the level after the first dose. In patients receiving a retreatment cycle (n = 11)[8] and in patients receiving an additional cycle (n = 7),[9] C_{max} and AUC_{0-28} tended to be lower than that in the first cycle.

The relationship between the biological disposition and efficacy of Breyanzi was investigated. Median C_{max} and median AUC_{0-28} were 33,121.6 copies/μg and 258,584.8 day•copies/μg, respectively, in responded patients (n = 175), and 8,160.0 copies/μg and 99,966.3 day•copies/μg, respectively, in non-responded patients (n = 50). Median t_{max} was 11.0 days in responded patients and 14.0 days in

7) The second dose was administered 14 days after the first dose.

8) In the retreatment cycle, the second dose of Breyanzi was administered to patients whose best overall response (BOR) was progressive disease (PD) after complete response (CR) achieved by Breyanzi. The second dose was administered 14 days after the first dose.

9) In the additional cycle, an additional dose of Breyanzi was administered to patients whose BOR was stable disease (SD) or partial response (PR) after the first efficacy assessment.

non- responded patients.

The relationship between the biological disposition and safety of Breyanzi was investigated. Median C_{max} and median AUC_{0-28} were 43,756.1 copies/μg and 380,670.8 day•copies/μg, respectively, in patients with cytokine release syndrome (CRS) (all grades; n = 95), and 18,937.0 copies/μg and 157,771.7 day•copies/μg, respectively, in patients without CRS (n = 143). Similarly, median C_{max} and median AUC_{0-28} were 66,606.6 copies/μg and 622,692.3 day•copies/μg, respectively, in patients with investigator-identified neurotoxicity (iiNT) (all grades) and 19,235.9 copies/μg and 160,665.9 day•copies/μg, respectively, in patients without iiNT.

Based on the above, the applicant explained that C_{max} and AUC_{0-28} tended to be higher in responded patients than in non-responded patients, and, similarly, C_{max} and AUC_{0-28} tended to be higher in patients with CRS or iiNT than in patients without CRS or iiNT.

Table 14. Parameters of biological disposition of Breyanzi-derived gene by dosage regimen in Study 017001

	DL1S	DL2S	DL3S	DL2D
C_{max} (copies/μg)	25,098.5	20,958.2	23,548.8	8,734.0
t_{max} (day)	11.0	14.0	10.0	1.0
AUC_{0-28} (day•copies/μg)	229,062.6	186,994.0	185,393.9	106,443.8

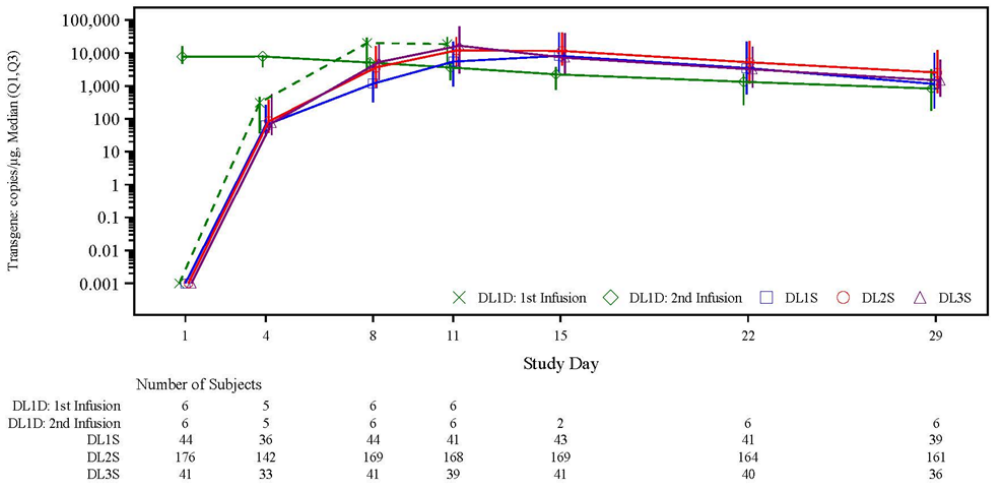

Figure 1. Change over time in the level of Breyanzi-derived gene by dosage regimen in Study 017001

5.2.2 Study BCM-001 (CTD 5.3.5.2-3)

Change over time in the level of Breyanzi-derived gene in the peripheral blood was investigated in 35 patients with relapsed or refractory B-cell NHL in Study BCM-001. In this study, 100×10^6 cells of Breyanzi (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells) were administered as a single dose. The Breyanzi-derived gene level in the peripheral blood was measured by qPCR (detection limit, 5 copies/reaction) using peripheral blood samples collected at baseline and 1, 4, 8, 11, 15, 22, 29, 60, 90, 180, 270, 365, 545, and 730 days after Breyanzi infusion. C_{max}, AUC_{0-28}, and t_{max} of Breyanzi were calculated for patients in whom peripheral blood Breyanzi-derived gene was detected 29 days after infusion or later.

Figure 2 shows the change over time in the Breyanzi-derived gene level in the peripheral blood, and

Table 15 shows the median values of the PK parameters of biological disposition, calculated by Breyanzi-derived gene level in the peripheral blood.[10)] The applicant explained that the parameters of biological disposition showed a similar tendency in Cohort 1 consisting of European patients and in Cohort 3 consisting of Japanese patients.

The relationship between the biological disposition and the efficacy of Breyanzi was investigated. In Cohort 1, the median C_{max} and the median $AUC_{0\text{-}28}$ was 20,875.0 copies/μg and 209,244.6 day•copies/μg, respectively, in responded patients (n = 22) and 35,331.0 copies/μg and 354,984.3 day•copies/μg, respectively, in non-responded patients (n = 12). In Cohort 3, the median C_{max} and the median $AUC_{0\text{-}28}$ was 63,569.0 copies/μg and 319,880.8 day•copies/μg, respectively, in responded patients (n = 7) and 29,554.0 copies/μg and 476,366.9 day•copies/μg, respectively, in non-responded patients (n = 3).

The relationship between the biological disposition and the safety of Breyanzi was investigated.[11)] In Cohort 1, the median C_{max} and the median $AUC_{0\text{-}28}$ were 38,472.0 copies/μg and 490,595.7 day•copies/μg, respectively, in patients with CRS (all grades; n = 12) and 25,641.0 copies/μg and 220,287.6 day•copies/μg, respectively, in patients without CRS (n = 22). In Cohort 1, the median C_{max} and the median $AUC_{0\text{-}28}$ were 49,474.5 copies/μg, and 490,595.7 day•copies/μg, respectively, in patients experiencing neurotoxicity (all grades; n = 6) and 25,641.0 copies/μg and 220,287.6 day•copies/μg, respectively, in patients without neurotoxicity (n = 28). In Cohort 3, the median C_{max} and the median $AUC_{0\text{-}28}$ were 63,569.0 copies/μg and 534,192.1 day•copies/μg, respectively, in patients experiencing CRS (all grades; n = 5) and 29,554.0 copies/μg and 319,880.8 day•copies/μg, respectively, in patients without CRS (n = 5). In Cohort 3, the patient experiencing neurotoxicity (all grades, n = 1) showed C_{max} of 63,569.0 copies/μg, and $AUC_{0\text{-}28}$ of 692,060.0 day•copies/μg whereas, in patients without neurotoxicity (n = 9), the median C_{max} was 29,554.0 copies/μg and median $AUC_{0\text{-}28}$ was 319,880.8 day•copies/μg.

The applicant explained that Study BCM-001 showed similar tendencies in the relationship between the biological disposition and the efficacy or safety of Breyanzi to those in Study 017001, despite the limited number of patients participated and inter-individual variability observed in the parameters of the biological disposition.

Table 15. Parameters of biological disposition of Breyanzi-derived gene by cohort in Study BCM-001

	Cohort 1 (Europe)	Cohort 3 (Japan)	Total
C_{max} (copies/μg)	28,004.0	46,561.5	29,414.5
t_{max} (day)	10.0	12.0	10.0
$AUC_{0\text{-}28}$ (day•copies/μg)	298,106.0	398,123.9	325,344.6

[10)] Data cut-off on September 13, 2019
[11)] Data cut-off on June 19, 2020

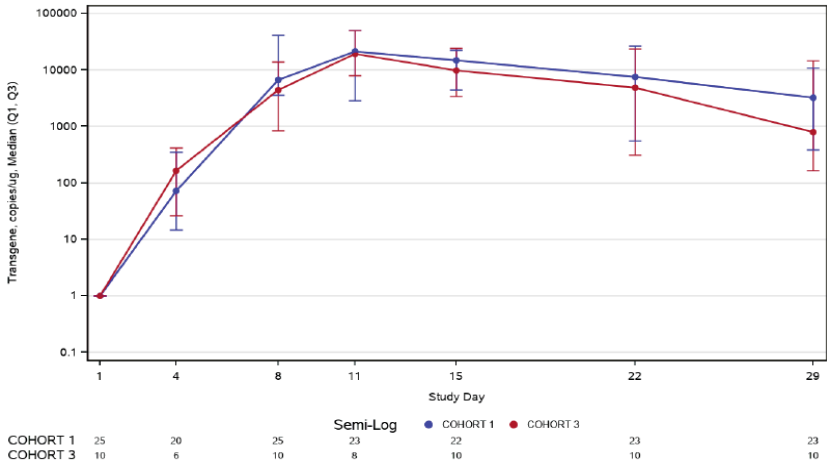

Figure 2. Change over time in the level of Breyanzi-derived gene by cohort in Study BCM-001

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation of the biological disposition of Breyanzi is acceptable.

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

The applicant submitted evaluation data on the efficacy and safety from 1 foreign phase I study and 1 global phase II study (Table 16).

Table 16. List of clinical studies for efficacy and safety

Data category	Region	Study	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	017001	I	Patients with relapsed or refractory B-cell NHL	427	Intravenous administration of anti-CD19 CAR T cells at the following doses: DL1S: A single dose of 50×10^6 cells DL2S: A single dose of 100×10^6 cells DL3S: A single dose of 150×10^6 cells DL1D: 2 doses of 50×10^6 cells each	Efficacy Safety
	Global	BCM-001	II	Patients with relapsed or refractory aggressive B-cell NHL	69	A single intravenous dose of 100×10^6 anti-CD19 CAR T cells	Efficacy Safety

Each clinical study is summarized below. The main adverse events excluding deaths observed in each clinical study are presented in Section "8. Adverse Events Observed in Clinical Studies."

6.1 Evaluation data

6.1.1 Foreign clinical study

6.1.1.1 Foreign phase I study (CTD 5.3.5.2-1 and 5.3.5.2-2; Study 017001, ongoing since January 2016 [data cut-off on August 12, 2019])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of Breyanzi in

patients with relapsed or refractory B-cell NHL (target sample size, 274 patients [174 in total in the DE and DF groups, 100 in the DC group]) at 14 study sites in the US. Table 17 shows the main inclusion/exclusion criteria.

Table 17. Main inclusion/exclusion criteria

Inclusion criteria • Patients with relapsed or refractory B-cell NHL with any of the following tissue type: ➢ DLBCL cohort: Patients diagnosed with DLBCL,* HGBCL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, or FL3B and received an anthracycline and rituximab (or other CD20-targeted agent) as well as ≥2 lines of chemotherapy or autologous HSCT. ➢ MCL cohort: Patients with MCL with ≥1 line of prior chemotherapy • Patients with PET-positive disease according to Lugano response criteria (*J Clin Oncol*. 2014;32:3059-68) • Patients with ECOG PS score of 0 or 1** Exclusion criteria • Patients who received prior treatment with autologous HSCT within 90 days before leukapheresis, treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis • Patients who received prior CAR T-cell therapy or other genetically-modified T-cell therapy • Patients with CNS-only involvement by malignancy

* *de novo* or transformed indolent non-Hodgkin lymphoma (tiNHL)

** Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2 was eligible according to the fifth or earlier revision of the study protocol.

The study had the following 2 cohorts:

- DLBCL cohort: Patients with DLBCL, high grade B-cell lymphoma (HGBCL), PMBCL, or follicular lymphoma grade 3B (FL3B) with ≥2 lines of prior chemotherapy
- Mantle cell lymphoma (MCL) cohort: Patients with MCL with ≥1 line of prior chemotherapy

Patients in each cohort were assigned to the DF, DE, or DC group; the objective in each group was as follows:

- DF group: Using mCRM (*Contemp Clin Trials*. 2016;48:153-165), dose-limiting toxicity (DLT) and complete response (CR) were estimated for each dose to assess dosage regimen or method of use required to achieve optimal anti-tumor effect and to secure safety.
- DE group: The efficacy and safety of Breyanzi were evaluated using the dosage regimen or method of use that was confirmed to be safe and effective in the DF group.
- DC group: Based on the information obtained in the DF and DE groups, the safety and efficacy of Breyanzi under the dosage regimen or method of use recommended by the study steering committee were further evaluated.

The study consisted of a pre-treatment phase (period from leukapheresis to LD chemotherapy and Breyanzi manufacturing period after screening), treatment phase (from the start of LD chemotherapy to Day 29 after Breyanzi infusion), post-treatment follow-up phase (30 days to 2 years after Breyanzi infusion), and the long-term follow-up (up to 15 years after Breyanzi infusion).

In order to facilitate the engraftment and growth of Breyanzi in the body, Breyanzi infusion was preceded by a pretreatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 once daily for 3 days. Breyanzi was infused 2 to 7 days after the completion of LD chemotherapy. While Breyanzi was in the process of manufacture, the patient was allowed to receive an anti-cancer therapy for disease control (bridging chemotherapy). The bridging chemotherapy was required to be performed with a low-dose anti-cancer

agent (e.g., ≤300 mg/m^2 cyclophosphamide per day) and to be completed ≥7 days before the start of LD chemotherapy.

The dosage regimen of Breyanzi in the DF, DE, and DC groups was as shown below. CD8-positive T cells was the first to be infused intravenously separately followed by CD4-positive T cells.

Dosage regimen of Breyanzi
DL1S: A single intravenous dose of 50 × 10^6 anti-CD19 CAR T cells (25 × 10^6 CD8-positive T cells, 25 × 10^6 CD4-positive T cells)
DL2S: A single intravenous dose of 100 × 10^6 anti-CD19 CAR T cells (50 × 10^6 CD8-positive T cells, 50 × 10^6 CD4-positive T cells)
DL3S: A single intravenous dose of 150 × 10^6 anti-CD19 CAR T cells (75 × 10^6 CD8-positive T cells, 75 × 10^6 CD4-positive T cells)
DL1D: Intravenous dose of 50 × 10^6 anti-CD19 CAR T cells (25 × 10^6 CD8-positive T cells, 25 × 10^6 CD4-positive T cells), followed by the administration of the same dose on Day 14. LD chemotherapy was not performed before the second dose.

In this study, treatment groups (DF, DE, and DC groups) and the dosage regimen were added and determined in a stepwise manner. The sample sizes changed during the study. The details of the changes are as follows:

- The study began with the DF group alone using the DL1S regimen (the target sample size of the DF group, ≤70 patients)
- [redacted], 20[redacted]: The DL2S and DL1D regimens were added. The target sample size of the DF group was increased to ≤90 patients.
- [redacted], 20[redacted]: The DE group was added. The DL3S regimen was added. The target sample size of the DF group was increased to ≤114 patients, and the combined target sample size of the DF and DE groups was changed to ≤144 patients at the maximum.
- [redacted], 20[redacted]: The DC group was added. The target sample size of the DC group was determined as ≤100 patients, and the combined target sample size of the DF and DE groups was changed to ≤174 patients.
- [redacted], 20[redacted] and [redacted], 20[redacted]: In order to determine a recommended dosage regimen in the DC group of the DLBCL cohort, the efficacy and safety, etc., of DL1S and DL2S in the DF and DE groups were evaluated by the study steering committee according to the pre-specified procedure. The results showed that the overall response rate at 3 months after Breyanzi administration tended to be higher with DL2S than with DL1S, and the incidence of Grade ≥3 CRS or nerve disorder with DL2S did not tend to be higher than with DL1S. Therefore, the DL2S regimen was chosen to be recommended for the DC group in the DLBCL cohort, as per the advice of the study steering committee.
- [redacted], 20[redacted]: The target sample size of the DC group was changed to ≥100 patients.

A total of 427 patients were enrolled. Of 365 patients (341 in the DLBCL cohort, 24 in the MCL cohort), excluding 61 patients who failed the screening test and 1 patient who passed the screening test but did not give informed consent, 3 patients discontinued the study (DLBCL cohort, 1 died before

leukapheresis, 1 withdrew informed consent, 1 had not undergone leukapheresis at the data cut-off point). A total of 369 patients (344 in the DLBCL cohort, 25 in the MCL cohort), including 7 (6 in the DLBCL cohort, 1 in the MCL cohort) of the 61 patients who failed the screening test, underwent leukapheresis. After the leukapheresis, 57 patients withdrew from the study (50 in the DLBCL cohort; death due to disease progression in 33, disease-related complication in 6, failure to meet inclusion criteria in 3, ineligible for Breyanzi treatment in 2, consent withdrawal in 2, other in 2,[12)] manufacturing failure in 2: 7 in the MCL cohort; death due to disease progression in 3, ineligible for Breyanzi treatment in 3, failure to meet the eligibility criteria in 1). As a result, of 312 patients eligible for LD chemotherapy and Breyanzi administration (294 in the DLBCL cohort, 18 in the MCL cohort), 286 patients receiving Breyanzi (269 in the DLBCL cohort [45 with DL1S, 177 with DL2S, 41 with DL3S, 6 with DL1D], 17 in the MCL cohort [6 in DL1S, 11 in DL2S]) were included in the primary safety analysis population. A total of 26 patients receiving Breyanzi of substandard quality (out-of-specification product) (25 in the DLBCL cohort, 1 in the MCL cohort) were excluded from the primary safety analysis population. A DLT analysis was performed on 139 patients in the DF and DE groups in the DLBCL cohort.

Of 269 patients who received Breyanzi in the DLBCL cohort, 256 patients (40 with DL1S, 169 with DL2S, 41 with DL3S, 6 with DL1D) were included in the DLBCL efficacy analysis population, excluding 4 patients who did not show positron emission tomography (PET)-positive lesion before Breyanzi administration, 6 patients who underwent treatment for disease control but were not evaluated by PET or computed tomography (CT) before Breyanzi administration, and 3 patients who received Breyanzi manufactured by the method at the earliest development stage (Process v1). Of those, 133 patients with DL2S were included in the primary analysis set (PAS)[13)] that served as the primary efficacy analysis population.

The primary efficacy endpoint was overall response rate assessed by the independent review committee according to Lugano response criteria (*J Clin Oncol*. 2014;32:3059-68), which have been established and widely used as the criteria for evaluating NHL. The main efficacy analysis point in this study was the data cut-off point of April 12, 2019. Table 18 summarizes the results of the primary endpoint. The overall response rate [95% confidence interval (CI)] was 74.4% [66.2, 81.6], with the lower limit of the 95% CI exceeding the pre-specified threshold of the overall response rate (40%[14)]). Meanwhile, the overall response rate at the data cut-off of August 12, 2019 were not different from those at the data cut-off of April 12, 2019. Subsequent results are shown based on the data cut-off of August 12, 2019.

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12) One patient received palliative care due to rapid disease deterioration and another patient selected another treatment.

13) Among patients with DL2S of the DLBCL cohort, those with DLBCL or HGL who had no history of autologous HSCT, had ECOG PS score ≤1 before LD chemotherapy as well as PET-positive disease before Breyanzi infusion according to the assessment of the independent review committee, and received the conforming product. Patients who, after lymphoma treatment for disease control, did not undergo baseline PET/CT re-evaluation were excluded.

14) In patients with aggressive large B-cell lymphoma with a ≥2 lines of prior chemotherapy, the standard chemotherapy with a single or multiple drugs is shown to have achieved the overall response rate of 12% to 46% and the CR rate of 6% to 38% (*Lancet Oncol*. 2012;13:696-706, *Ann Hematol.* 2012;91:1013-1022, etc.). In the meta-analysis using these published reports, the overall response rate [95% CI] and the CR rate [95% CI] were estimated to be 30% [24, 38] and 19% [13, 26], respectively. According to a retrospective study in 636 patients with DLBCL, including those whose BOR to the chemotherapy was either PD or SD or who had relapsed DLBCL within 12 months after autologous HSCT, and who have a prior treatment with anti-CD20 monoclonal antibody (except in CD20-negative patients) plus anthracycline (*Blood*. 2017;130:1800-1808), the overall response rate (range) was 26% (21%-31%) and the CR rate (range) was 7% (3%-15%). Based on these results, the threshold for the overall response rate was determined to be 40%.

Table 18. Results of response rate
(assessed by the independent review committee, PAS, data cut-off on April 12, 2019)

	Number of patients (%)
	PAS (DL2S) (n = 133)
CR	72 (54.1)
PR	27 (20.3)
SD	13 (9.8)
PD	14 (10.5)
Non-PD*	2 (1.5)
Not evaluated	5 (3.8)
Overall response (CR + PR)	99
(Overall response rate [95% CI[a]] (%))	(74.4 [66.2, 81.6])

a Clopper-Pearson method
* For patients whose PET was unevaluable or not performed at all evaluation time points after baseline with the CT stage-based best response of CR, partial response (PR), or stable disease (SD), the best response was determined as non-progressive disease (PD) by the independent review committee. Non-PD was counted as "no response" for the calculation of the overall response rate.

Table 19 shows the results of the overall response rate in the DLBCL efficacy analysis population.

Table 19. Results of response rate (assessed by the independent review committee, DLBCL efficacy analysis population, data cut-off on August 12, 2019)

	Number of patients (%)				
	DL1S (n = 40)	DL2S (n = 169)	DL3S (n = 41)	DL1D (n = 6)	Total (n = 256)
CR	24 (60.0)	88 (52.1)	21 (51.2)	3 (50.0)	136 (53.1)
PR	3 (7.5)	37 (21.9)	9 (22.0)	1 (16.7)	50 (19.5)
SD	6 (15.0)	17 (10.1)	4 (9.8)	1 (16.7)	28 (10.9)
PD	4 (10.0)	17 (10.1)	6 (14.6)	1 (16.7)	28 (10.9)
Non-PD*	1 (2.5)	2 (1.2)	1 (2.4)	0	4 (1.6)
Not evaluated	2 (5.0)	8 (4.7)	0	0	10 (3.9)
Overall response (CR + PR)	27 (67.5)	125 (74.0)	30 (73.2)	4 (66.7)	186 (72.7)
(Overall response rate [95% CI[a]])	[50.9, 81.4]	[66.7, 80.4]	[57.1, 85.8]	[22.3, 95.7]	[66.8, 78.0]

a Clopper-Pearson method
* For patients whose PET was unevaluable or not performed at all evaluation time points after baseline with the CT stage-based best response of CR, PR, or SD, the best response was determined as non-PD by the independent review committee. Non-PD was counted as "no response" for the calculation of the overall response rate.

During the DLT evaluation period,[15)] DLT was observed in 9 of 139 patients in the DF and DE groups of the DLBCL cohort (6 with DL1S, 2 with DL2S, 1 with DL3S), and MTD was not reached.

Death occurred during the Breyanzi treatment period or within 30 days after the treatment in 3 of 269 patients in DLBCL safety analysis population. The causes of the deaths were diffuse alveolar damage, septic shock, and cardiomyopathy in 1 patient each. A causal relationship to Breyanzi could not be ruled out for diffuse alveolar damage[16)] and cardiomyopathy[17)] in 1 patient each. Furthermore, 6 patients died within 30 days after the last dose due to disease progression. Death due to adverse events occurred in 8 of 269 patients (3.0%) ≥31 days after the last dose of Breyanzi. The causes of deaths were progressive multifocal leukoencephalopathy in 2 patients, pulmonary haemorrhage, multiple organ dysfunction syndrome, leukoencephalopathy, myelodysplastic syndrome, septic shock, and death in 1 patient each. A causal relationship to Breyanzi could not be ruled out for progressive

15) 28 days after Breyanzi infusion. 28 days after the second dose in DL1D were also included in DLT evaluation period.
16) 8[redacted]-year-old men on the DL1S regimen with primary disease of DLBCL. Grade 3 *Streptococcal* bacteremia occurred 1 day after Breyanzi infusion, Grade 4 neutropenia 2 days after infusion, Grade 4 thrombocytopenia 3 days after infusion, and Grade 4 diffuse alveolar damage 18 days after infusion. The patient died 23 days after Breyanzi infusion.
17) 5[redacted]-year-old women on the DL2S regimen with primary disease of DLBCL. Grade 4 cardiomyopathy occurring 4 days after Breyanzi infusion caused cardiac arrest. The patient resuscitated and treated at ICU, but died 7 days after Breyanzi infusion.

multifocal leukoencephalopathy,[18)] pulmonary haemorrhage,[19)] and multiple organ dysfunction syndrome[20)] in 1 patient each. A total of 99 patients died of disease progression, 3 patients due to other causes (stroke unrelated to the study, pneumonia, and diffuse intra-abdominal ischaemia), and 4 patients for an unknown cause ≥31 days after the last dose of Breyanzi.

Among 17 patients receiving Breyanzi in the MCL cohort, 1 patient died during Breyanzi treatment period or within 30 days after a dose of Breyanzi. The cause of the death was tumor lysis syndrome (TLS),[21)] and its causal relationship to Breyanzi could not be ruled out. One patient died due to an adverse event ≥31 days after the last dose of Breyanzi. The cause of death was diffuse alveolar damage, and its causal relationship to Breyanzi was ruled out.

6.1.2 Global study

6.1.2.1 Global phase II study (CTD 5.3.5.2-3, Study BCM-001, ongoing since June 2018 [data cut-off on June 19, 2020])

An open-label, uncontrolled, global phase II study was conducted to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory aggressive B-cell NHL (target sample size, 72 patients [34 in cohort 1, 28 in cohort 2, 10 in cohort 3]) at 14 study sites in Japan and foreign countries. Table 20 shows the main inclusion/exclusion criteria.

Table 20. Main inclusion/exclusion criteria

Inclusion criteria • Patients with relapsed or refractory B-cell NHL with any of the following tissue types: ➢ Cohort 1: Patients diagnosed with DLBCL,* HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, or FL3B according to WHO classification (2016) (*Blood*. 2016;127:2375-90) who had received ≥2 lines of chemotherapy including anthracycline drug and rituximab (or any other drug targeting CD20). ➢ Cohort 2: Patients diagnosed with DLBCL* or HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, or FL3B according to WHO classification (2016) (*Blood*. 2016;127:2375-90) who had received 1 line of chemotherapy including anthracycline drug and rituximab (or any other drug targeting CD20) and are ineligible for HSCT. ➢ Cohort 3 (in Japan only): Patients who meet the inclusion criteria of Cohort 1 or 2 • Patients with histologically confirmed recent relapse • Patients with ECOG PS of 0 or 1** Exclusion criteria • Patients who received CD19-targeted therapy in the past. Patients who received HSCT in the past (Cohort 2 only). • Patients with T-cell/histiocyte-rich large B-cell lymphoma, primary cutaneous large B-cell lymphoma, PMBCL, age-related EBV-positive DLBCL, or Burkitt's lymphoma

* *de novo* or transformed follicular lymphoma (TFL)

** According to the clinical study protocol ver. 2, patients with ECOG PS score of 2 were allowed to be enrolled in Cohorts 2 or 3 only if they were ineligible for high-dose chemotherapy and HSCT due to age, systemic conditions, or comorbidities, and met to all other inclusion/exclusion criteria.

The study consisted of a pretreatment phase (screening, from leukapheresis through LD chemotherapy,

18) 6[redacted]-year-old woman on the DL2S regimen with primary disease of DLBCL. The patient experienced progressive multifocal leukoencephalopathy 710 days after Breyanzi infusion and died 775 days after infusion.

19) 6[redacted]-year-old man on the DL2S regimen with primary disease of HGBCL. The patient experienced Grade 4 CRS 4 days after Breyanzi infusion, Grade 4 acute respiratory failure 6 days after infusion, Grade 4 acute renal dysfunction 12 days after infusion, Grade 4 gastrointestinal haemorrhage 23 days after infusion, Grade 4 pulmonary haemorrhage 31 days after infusion. The patient died 33 days after infusion.

20) 7[redacted]-year-old man on the DL2S regimen with primary disease of HGBCL. Grade 3 neutropenia and thrombocytopenia were observed before Breyanzi infusion. Thrombocytopenia progressed to Grade 4 6 days after infusion and neutropenia to Grade 4 8 days after infusion, but both improved by medication. The patient experienced Grade 2 pneumonia 78 days after infusion and, despite treatment, Grade 4 sepsis occurred 82 days after infusion. The patient underwent mechanical ventilation but suffered multiple organ dysfunction syndrome and died 85 days after infusion.

21) 7[redacted]-year-old man with primary disease of MCL. The patient experienced Grade 2 acute renal dysfunction 9 days after Breyanzi infusion, and Grade 2 shock, Grade 2 CRS, and Grade 4 TLS 10 days after infusion. The patient underwent continuous hemodialysis and hemodynamic control at an ICU, but CRS progressed to Grade 4, resulting in death 12 days after infusion.

and Breyanzi manufacturing), a treatment phase (from the start of LD chemotherapy through 29 days after Breyanzi infusion), and a post-treatment follow-up phase (30 days to 2 years after Breyanzi infusion).

Breyanzi was infused intravenously as a single dose of 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells).

In order to facilitate the engraftment and growth of Breyanzi in the body, Breyanzi infusion was preceded by a pretreatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 and fludarabine 300 mg/m^2 once daily for 3 days. Breyanzi was infused 2 to 7 days after the completion of LD chemotherapy. While Breyanzi was in the process of manufacture, the patient was allowed to receive an anti-cancer therapy for disease control (bridging chemotherapy). The bridging chemotherapy was required to be performed with a low-dose anti-cancer agent (e.g., ≤300 mg/m^2 cyclophosphamide per day) and to be completed ≥7 days before the start of LD chemotherapy. Patients were eligible for the bridging chemotherapy only if they had a PET-positive lesion and met the relevant qualification criteria before LD chemotherapy and Breyanzi infusion.

A total of 69 patients were enrolled in Cohorts 1 and 3 (53 in Cohort 1, 16 in Cohort 3), from which 10 patients who failed the screening test were excluded. The remaining 59 patients (45 in Cohort 1, 14 in Cohort 3) received leukapheresis, and then 8 patients discontinued the study (4 due to death caused by disease progression, 1 due to adverse event [Grade 4 neutropenic sepsis which occurred after bridging chemotherapy], 2 due to failure to meet the inclusion criteria, 1 due to manufacturing failure). As a result, 46 patients (36 in Cohort 1, 10 in Cohort 3) who had received Breyanzi after LD chemotherapy were included in the primary efficacy and safety analysis population. A total of 5 patients receiving Breyanzi of substandard quality (out-of-specification product) were excluded from the primary efficacy and safety analysis population. During the study, the supply of viral vector necessary for the manufacture of Breyanzi was constrained due to the change of supplier. For this reason, patients were preferentially enrolled in Cohort 1, resulting in no enrollment of patients in Cohort 2.

The primary endpoint was the overall response rate assessed by the independent review committee based on Lugano response criteria (*J Clin Oncol.* 2014;32:3059-68). The main time point of efficacy analysis in this study was at the data cut-off on September 13, 2019.[22)] Table 21 shows the results of the primary endpoint. The overall response rate [95% CI] was 58.8% [40.7, 75.4], which was significantly higher than the threshold (40%).[23)] The overall response rate [95% CI] in Cohort 3 (10

22) The primary efficacy analysis was performed at the time point when the sum of efficacy-evaluable patients in Cohorts 1, 2, and 3 reached 34, after the conforming product was administered to ≥10 Japanese patients in Cohort 3, who were followed up for ≥3 months or until death, PD, or treatment discontinuation.

23) In patients with aggressive large B-cell lymphoma with a ≥2 lines of prior chemotherapy, the standard chemotherapy with a single or multiple drugs is shown to have achieved the overall response rate of 12% to 46% and the CR rate of 6% to 38% (*Lancet Oncol*. 2012;13:696-706, *Ann Hematol.* 2012;91:1013-1022, etc.). In the meta-analysis using the data from these published reports, the overall response rate [95% CI] and the CR rate [95% CI] were estimated to be 30% [24, 38] and 19% [13, 26], respectively. Taking into account that relapsed or refractory conditions are prognostic factors, a weighted statistical estimation was performed in the patients subjected to the above meta-analysis. For the estimation, the patients were classified into either relapsed or refractory patients, and the distribution of patients (relapsed patients 55%, refractory patients 45%) obtained from the preliminary analysis of Study 017001 was used (*Blood Cancer J.* 2016;6:e473). The overall response rate [95% CI] was 28% [16%, 40%], and the CR rate [95% CI] was 14% [6%, 24%]. These results suggested that the overall response rate in conventional treatments does not exceed 40%. Accordingly, the threshold was determined to be 40%.

Japanese patients) was 70.0% [34.8, 93.3].

Table 21. Results of response rate
(assessed by the independent review committee, data cut-off on September 13, 2019)

	Number of patients		
	Cohort 1 (n = 24)	Cohort 3 (n = 10)	Total (n = 34)
CR	7 (29.2)	5 (50.0)	12 (35.3)
PR	6 (25.0)	2 (20.0)	8 (23.5)
SD	6 (25.0)	0	6 (17.6)
Non-PD*	1 (4.2)	0	1 (2.9)
PD	4 (16.7)	3 (30.0)	7 (20.6)
Overall response (CR + PR)	13 (54.2)	7 (70.0)	20 (58.8)
(Overall response rate [95% CI[a]])	[32.8, 74.4]	[34.8, 93.3]	[40.7, 75.4]
One-sided P value[b]	-	-	0.020

a Clopper-Pearson method
b Significance level of 0.025 (one-sided), exact binominal test
* For patients whose PET was unevaluable or not performed at all evaluation time points after baseline with CT stage-based best response of CR, PR, or SD, the best response was determined as non-PD by the independent review committee. Non-PD was counted as "no response" for the calculation of the overall response rate.

Table 22 shows the results of response rates as of the data cut-off on June 19, 2020. The overall response rate [95% CI] was 63.0% [47.5, 76.8]. The overall response rate [95% CI] in Cohort 3 (10 Japanese patients) was 70.0% [34.8, 93.3].

Table 22. Results of response rates
(assessed by independent review committee, data cut-off on June 19, 2020)

	Number. of patients		
	Cohort 1 (n = 36)	Cohort 3 (n = 10)	Total (n = 46)
CR	12 (33.3)	5 (50.0)	17 (37.0)
PR	10 (27.8)	2 (20.0)	12 (26.1)
SD	7 (19.4)	0	7 (15.2)
Non-PD*	1 (2.8)	0	1 (2.2)
PD	6 (16.7)	3 (30.0)	9 (19.6)
Overall response (CR + PR)	22 (61.1)	7 (70.0)	29 (63.0)
(Overall response rate [95% CI[a]])	[43.5, 76.9]	[34.8, 93.3]	[47.5, 76.8]

a Clopper-Pearson method
* For patients whose PET was unevaluable or not performed at all evaluation time points after baseline with the CT stage-based best response of CR, PR, or SD, the best response was determined as non-PD by the independent review committee. Non-PD was counted as "no response" for the calculation of the overall response rate.

Death due to adverse event occurred in 1 patient (Cohort 1) within 30 days after the last dose. The cause of the death was respiratory failure,[24)] and its causal relationship to Breyanzi could not be ruled out. Death due to disease progression did not occur within 30 days after the last dose. Death due to adverse events occurred ≥31 days after the last dose of Breyanzi in 2 patients (1 each in Cohort 1 and Cohort 3). The cause of death was Candida sepsis and multiple organ dysfunction syndrome in 1 patient each. A causal relationship to Breyanzi could not be ruled out for Candida sepsis[25)] in 1 patient. A total of 19 patients died due to disease progression on or ≥31 days after the last dose.

24) 6[redacted]-year-old man with primary disease of DLBCL. The patient presented with Grade 2 capillary leak syndrome, Grade 2 confusional state, and Grade 3 edema peripheral 2 days after Breyanzi infusion, and Grade 3 CRS 4 days after infusion. He was admitted to ICU due to the progression of neurological symptom 6 days after infusion. CRS and capillary leak syndrome progressed to Grade 4 7 days after infusion. Grade 4 respiratory failure occurred 11 days after infusion followed by Grade 4 Candida sepsis 14 days after infusion. The patient died of respiratory failure 15 days after infusion.

25) 5[redacted]-year-old man with primary disease of DLBCL. The patient had Grade 1 CRS 3 days after Breyanzi infusion. Due to CRS progressed to Grade 3 5 days after infusion, the patient was admitted to ICU. CRS resolved but convulsive seizure occurred 13 days after infusion, followed by Grade 4 histiocytosis hematophagic and macrophage activation syndrome 19 days after infusion and sepsis 22 days after infusion. The patient was diagnosed to have Grade 4 Candida sepsis 29 days after infusion and died 43 days after infusion.

6.R Outline of the review conducted by PMDA

6.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the DLBCL cohort in phase II part of Study 017001, and Cohorts 1 and 3 in Study BCM-001 were important in evaluating the efficacy and safety of Breyanzi. The efficacy and safety review primarily focused on these data.

The efficacy and safety of Breyanzi in Japanese patients were evaluated based on the data of Cohort 3 in Study BCM-001.

6.R.2 Efficacy

As a result of the following review, PMDA has concluded that Breyanzi was shown to have efficacy to a certain extent in patients with relapsed or refractory DLBCL, PMBCL, HGBCL, transformed indolent non-Hodgkin lymphoma (tiNHL), and FL3B.

6.R.2.1 Efficacy endpoint and evaluation results

The applicant's explanation about the efficacy of Breyanzi in patients with relapsed or refractory large B-cell lymphoma:

The primary endpoint of Studies 017001 and BCM-001 was overall response rate. Good response to Breyanzi will lead to tumor shrinkage, improved associated symptoms, and delayed relapse (disease progression), which can contribute to prolonged overall survival (OS) (B*one Marrow Transplant.* 2016;51:51-7). Therefore, overall response rate was selected as the primary endpoint. The overall response rate was defined as the percentage of patients whose best response was CR or partial response (PR) assessed by the independent review committee based on Lugano response criteria (*J Clin Oncol.* 2014 32:3059-68), the widely used definition that has been established as an efficacy evaluation method for treatment of NHL.

In Study 017001, the overall response rate [95% CI] (%) in PAS (n = 133) at the main time point of efficacy analysis (data cut-off on April 12, 2019) was 74.4% [66.2, 81.6], which exceeded the pre-determined threshold efficacy level (40%). As of the cut-off point of August 12, 2019, the overall response rate [95% CI] in the DLBCL efficacy analysis population (n = 256) was 72.7% [66.8, 78.0].

The median duration of response (DOR) [95% CI] (months) as of the cut-off time point of August 12, 2019 was not estimable [8.6, not estimable] and the median OS [95% CI] (months) was 21.1 [13.3, not estimable]. (Figure 3).

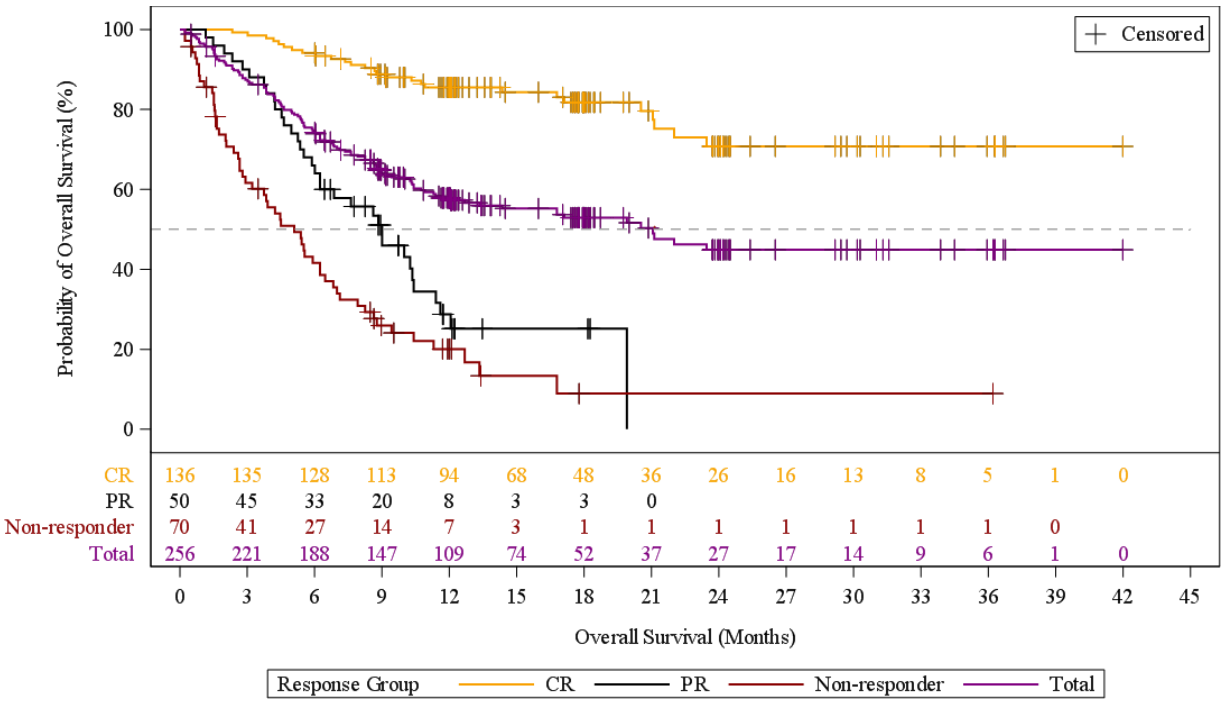

Figure 3. Kaplan-Meier curves of OS by response in DLBCL cohort of Study 17001 (DLBCL efficacy analysis population, data cut-off on August 12, 2019)

As of the main time point of efficacy analysis in Study BCM-001 (data cut-off on September 13, 2019), the overall response rate [95% CI] was 58.8% [40.7, 75.4], which was significantly greater than the threshold (40%). As of the cut-off time point of June 19, 2020, the overall response rate [95% CI] in Cohorts 1 and 3 was 63.0% [47.5, 76.8]. The median DOR [95% CI] (months) was 8.38 [2.23, not estimable]. The median OS [95% CI] (months) was 14.7 [6.28, not estimable].

In the meta-analysis[26)] using reports from clinical studies on patients with relapsed or refractory large B-cell lymphoma with a ≥2 lines of prior chemotherapy (*Lancet Oncol.* 2012;13:696-706, *Lancet Haematol.* 2019;6:e254-e265, etc.), the overall response rate [95% CI] was 31.2% [25.3%, 37.8%], and the range of the median OS was 3.4 to 9.4 months, which indicates that the efficacy of Breyanzi was demonstrated by Studies 017001 and BCM-001.

In Cohort 3 (10 Japanese patients) of Study BCM-001, the overall response rate was 70.0% (rate of CR 50.0%, rate of PR 20.0%). The median DOR [95% CI] (months) was 9.07 [2.10, not estimable] and the median OS [95% CI] (months) was 14.72 [1.71, not estimable]. These results indicate promising efficacy of Breyanzi in Japanese patients.

PMDA asked the applicant to explain the efficacy of Breyanzi by tissue type.

The applicant's explanation:
Tables 23 and 24 show the results of the response rate by tissue type in Studies 017001 and BCM-001.

26) Clinical studies reporting a response rate to chemotherapy of patients with relapsed or refractory large B-cell lymphoma with a ≥2 lines of prior chemotherapy were retrieved from articles published from January 2000 through April 2019 in databases such as Medline, Embase, and CDSR and from websites of American Society of Clinical Oncology, etc., based on keywords such as "Diffuse large B cell lymphoma" and "DLBCL."

Although the results are subject to careful interpretation because of the small number of subjects with some tissue types, clinically significant efficacy was observed in all tissue types, each of which showing consistency with the overall population.

Table 23. Efficacy by tissue type
(DLBCL cohort in Study 017001, data cut-off on August 12, 2019)

		DLBCL	HGBCL	tiNHL		FL3B	PMBCL	Overall
				TFL	Other than TFL			
		(n = 131)	(n = 33)	(n = 57)	(n = 18)	(n = 3)	(n = 14)	(n = 256)
Overall response rate	CR + PR n (%)	89 (67.9)	25 (75.8)	48 (84.2)	11 (61.1)	2 (66.7)	11 (78.6)	186 (72.7)
	[95% CI[a]]	[59.2, 75.8]	[57.7, 88.9]	[72.1, 92.5]	[35.7, 82.7]	[9.4, 99.2]	[49.2, 95.3]	[66.8, 78.0]
Rate of CR	CR n (%)	64 (48.9)	20 (60.6)	36 (63.2)	7 (38.9)	2 (66.7)	7 (50.0)	136 (53.1)
	[95% CI[a]]	[40.0, 57.7]	[42.1, 77.1]	[49.3, 75.6]	[17.3, 64.3]	[9.4, 99.2]	[23.0, 77.0]	[46.8, 59.4]

a Clopper-Pearson method

Table 24. Efficacy by tissue type
(Study BCM-001, data cut-off on June 19, 2020)

		DLBCL	HGBCL	tiNHL (TFL only)	FL3B	Overall
		(n = 30)	(n = 4)	(n = 10)	(n = 2)	(n = 46)
Overall response rate	CR + PR n (%)	17 (56.7)	2 (50.0)	8 (80.0)	2 (100)	29 (63.0)
	[95% CI[a]]	[37.4, 74.5]	[6.8, 93.2]	[44.4, 97.5]	[15.8, 100]	[47.5, 76.8]
Rate of CR	CR n (%)	9 (30.0)	2 (50.0)	4 (40.0)	2 (100)	17 (37.0)
	[95% CI[a]]	[14.7, 49.4]	[6.8, 93.2]	[12.2, 73.8]	[15.8, 100.0]	[23.2, 52.5]

a Clopper-Pearson method

Study BCM-0001 did not investigate PMBCL and tiNHL (other than transformed follicular lymphoma [TFL]), and Study BCM-001 did not enroll Japanese patients with HGBCL. Given these, there are no data demonstrating the efficacy of Breyanzi in Japanese patients with these conditions. Nevertheless, the applicant explains that Breyanzi is expected to be effective in Japanese patients based on the following observations:

- CD19 is expressed in almost all large B-cell lymphoma including PMBCL, tiNHL (other than TFL), and HGBCL (*Am J Hematol.* 2016;91:E436-41, *Am J Pathol*. 1995;146:735-41, etc.). Breyanzi is considered to have efficacy against these tissue types as well, based on its mechanism of action.
- PMBCL, tiNHL (other than TFL), and HGBCL do not show a significant difference in patient characteristics, disease characteristics, diagnosis, or treatment algorithm between Japan and foreign countries, according to the Japanese and foreign clinical practice guidelines.
- In Studies 017001 and BCM-001 (non-Japanese patients), Breyanzi was similarly effective against PMBCL, tiNHL (other than TFL), and HGBCL as against other tissue types.

PMDA's view:

The above explanation of the applicant is understandable. Based on the results of Studies BCM-001 and 017001, Breyanzi has efficacy to a certain extent against relapsed or refractory DLBCL, PMBCL, HGBCL, tiNHL, and FL3B.

6.R.3 Safety (for adverse events, see Section "8. Adverse Events Observed in Clinical Studies")

As a result of the following review, PMDA identified adverse events requiring special attention in the use of Breyanzi, which are CRS, hemophagocytic lymphohistiocytosis, nerve disorder, infection, bone marrow depression, hypersensitivity, hypogammaglobulinemia, and TLS, and concluded that caution should be exercised against these adverse events.

PMDA also concluded that Breyanzi is tolerable, given appropriate measures i.e., monitoring and management of adverse events taken by a physician with sufficient knowledge and experience in the treatment of DLBCL, PMBCL, HGBCL, tiNHL, and FL3B at a medical institution well-equipped for dealing with these adverse events.

6.R.3.1 Safety profile of Breyanzi and differences in the safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety of Breyanzi:

Table 25 shows the summary of the safety in Study 017001 (DLBCL cohort) (data cut-off on August 12, 2019).

Table 25. Summary of safety (Study 017001 [DLBCL cohort])

	Number of patients (%) (n = 269)
All adverse events	267 (99.3)
Grade ≥ 3 adverse events	213 (79.2)
Serious adverse events	122 (45.4)
Adverse events resulting in death	7 (2.6)

Table 26 shows adverse events with an incidence of ≥20% in Study 017001 (DLBCL cohort).

Table 26. Adverse events with an incidence of ≥20% (Study 017001 [DLBCL cohort])

System organ class PT (MedDRA ver. 21.0)	Number of patients (n = 269)	
	All Grades	Grade ≥3
All adverse events	267 (99.3)	213 (79.2)
Blood and lymphatic system disorders		
Neutropenia	169 (62.8)	161 (59.9)
Anaemia	129 (48.0)	101 (37.5)
Thrombocytopenia	84 (31.2)	72 (26.8)
General disorders and administration site conditions		
Fatigue	119 (44.2)	4 (1.5)
Gastrointestinal disorders		
Nausea	90 (33.5)	4 (1.5)
Diarrhoea	71 (26.4)	1 (0.4)
Constipation	62 (23.0)	0
Vomiting	56 (20.8)	1 (0.4)
Nervous system disorders		
Headache	80 (29.7)	3 (1.1)
Dizziness	60 (22.3)	1 (0.4)
Metabolism and nutrition disorders		
Decreased appetite	76 (28.3)	7 (2.6)
Respiratory, thoracic and mediastinal disorders		
Cough	57 (21.2)	0
Immune system disorders		
Cytokine release syndrome	113 (42.0)	6 (2.2)

System organ class PT (MedDRA ver. 21.0)	Number of patients (n = 269)	
	All Grades	Grade ≥3
Vascular disorders		
Hypotension	60 (22.3)	8 (3.0)

In Study 017001 (DLBCL cohort), serious adverse events with an incidence of ≥3% were cytokine release syndrome in 44 patients (16.4%), encephalopathy in 14 patients (5.2%), neutropenia in 11 patients (4.1%), febrile neutropenia (FN), thrombocytopenia, and pyrexia in 10 patients (3.7%) each, aphasia in 9 patients (3.3%). pneumonia, confusional state, and hypotension in 8 patients (3.0%) each. A causal relationship to Breyanzi could not be ruled out for cytokine release syndrome in 44 patients, encephalopathy in 12 patients, aphasia in 9 patients, confusional state in 8 patients, neutropenia and thrombocytopenia in 6 patients each, FN in 5 patients, pneumonia and hypotension in 4 patients each, and pyrexia in 2 patients.

After Breyanzi infusion, deaths occurred in 122 patients (45.4%) (due to disease progression in 105 patients, adverse events in 10 patients, unknown cause in 4 patients [including 1 patient with death as a reported adverse event], and other in 3 patients [stroke unrelated to the study, pneumonia, and diffuse intra-abdominal ischaemia]).

Table 27 shows the summary of safety in Study 017001 (MCL cohort) (data cut-off on August 12, 2019). Serious adverse events observed in ≥2 patients were cytokine release syndrome in 4 patients. A causal relationship to Breyanzi could not be ruled out for all of these events.

Table 27. Summary of safety (Study 017001 [MCL cohort])

	Number of patients (%) (n = 17)
All adverse events	17 (100)
Grade ≥ 3 adverse events	14 (82.4)
Serious adverse events	10 (58.8)
Adverse events resulting in death	1 (5.9)

Table 28 shows the summary of safety in Study BCM-001 (Cohorts 1 and 3) (data cut-off on June 19, 2020).

Table 28. Summary of safety (Study BCM-001 [Cohorts 1 and 3])

	Number of patients (%)		
	Cohort 1 (n = 36)	Cohort 3 (n = 10)	Total (n = 46)
All adverse events	36 (100)	10 (100)	46 (100)
Grade ≥ 3 adverse events	34 (94.4)	9 (90.0)	43 (93.5)
Serious adverse events	18 (50.0)	2 (20.0)	20 (43.5)
Adverse events resulting in death	2 (5.6)	1 (10.0)	3 (6.5)

Table 29 shows adverse events with an incidence of ≥20% in Study BCM-001 (Cohorts 1 and 3).

Table 29. Adverse events with an incidence of ≥20% (Study BCM-001 [Cohorts 1 and 3])

System organ class PT (MedDRA ver. 21.0)	Number of patients	
	All Grades	Grade ≥3
All adverse events	46 (100)	43 (93.5)
Blood and lymphatic system disorders		
Neutropenia	41 (89.1)	39 (84.8)
Anaemia	26 (56.5)	18 (39.1)
Thrombocytopenia	25 (54.3)	16 (34.8)
Leukopenia	17 (37.0)	16 (34.8)
Immune system disorders		
Cytokine release syndrome	19 (41.3)	2 (4.3)
General disorders and administration site conditions		
Pyrexia	20 (43.5)	0

In Study BCM-001 (Cohorts 1 and 3), serious adverse events with an incidence of ≥10% were cytokine release syndrome in 7 patients (15.2%) and confusional state in 5 patients (10.9%), and their causal relationship to Breyanzi could not be ruled out.

Death occurred in 22 patients (disease progression in 19, adverse events in 3).

The applicant's explanation about the safety of Breyanzi by tissue type:
Table 30 shows the summary of safety by tissue type in Study 017001 (DLBCL cohort). All Grade adverse events with an incidence of ≥40% were neutropenia (DLBCL, 63.5%; HGBCL, 66.7%; TFL, 60.0%; tiNHL [non-TFL], 72.2%; FL3B, 100%; PMBCL, 40.0%), anaemia (50.4%, 41.7%, 45.0%, 61.1%, 33.3%, 40.0%), fatigue (44.5%, 33.3%, 51.7%, 33.3%, 66.7%, 46.7%), and CRS (42.3%, 38.9%, 43.3%, 44.4%, 0%, 46.7%). The only adverse event with a ≥20% higher incidence than in all other tissue types was thrombocytopenia (tiNHL [other than TFL], 55.6%).

Table 30. Summary of safety by tissue type (Study 01700, DLBCL cohort)

	Number of patients (%)			
	DLBCL	HGBCL	tiNHL	
			TFL	Non-TFL
	(n = 137)	(n = 36)	(n = 60)	(n = 18)
All adverse events	136 (99.3)	36 (100)	59 (98.3)	18 (100)
Grade ≥ 3 adverse events	108 (78.8)	30 (83.3)	48 (80.0)	14 (77.8)
Serious adverse events	65 (47.4)	14 (38.9)	24 (40.0)	9 (50.0)
Adverse events resulting in death	3 (2.2)	3 (8.3)	1 (1.7)	0
	FL3B	PMBCL	Total	
	(n = 3)	(n = 15)	(n = 269)	
All adverse events	3 (100)	15 (100)	267 (99.3)	
Grade ≥ 3 adverse events	3 (100)	10 (66.7)	213 (79.2)	
Serious adverse events	0	10 (66.7)	122 (45.4)	
Adverse events resulting in death	0	0	7 (2.6)	

Table 31 shows the summary of safety by tissue type in Study BCM-001. Adverse events of any grade with an incidence of ≥40% in the entire Study BCM-001 were neutropenia (DLBCL, 93.3%; HGBCL, 100.0%; TFL, 70.0%; FL3B, 100.0%), anaemia (56.7%, 75.0%, 60.0%, 0%), thrombocytopenia (56.7%, 50.0%, 60.0%, 0%), pyrexia (43.3%, 75.0%, 40.0%, 0%), and CRS (30.0%, 75.0%, 60.0%, 50.0%). The only adverse events with a ≥20% higher incidence than in other tissue types were pyrexia (HGBCL, 75.0%) and aphasia (HGBCL, 50.0%).

Table 31. Summary of safety by tissue type (Study BCM-001)

	Number of patients (%)				
	DLBCL (n = 30)	HGBCL (n = 4)	tiNHL (TFL only) (n = 10)	FL3B (n = 2)	Total (n = 46)
All adverse events	30 (100)	4 (100)	10 (100)	2 (100)	46 (100)
Grade ≥ 3 adverse events	29 (96.7)	4 (100)	8 (80.0)	2 (100)	43 (93.5)
Serious adverse events	12 (40.0)	4 (100)	4 (40.0)	0	20 (43.5)
Adverse events resulting in death	1 (3.3)	1 (25.0)	1 (10.0)	0	3 (6.5)

In Study 017001 (DLBCL cohort) and in Study BCM-001, no significant difference was observed in the incidence of adverse events among patients with different tissue types, although strict comparison is difficult due to the limited number of patients with some tissue types.

The applicant's explanation about the difference in the safety of Breyanzi between Japanese and non-Japanese patients:

Table 32 shows all grade and Grade ≥3 adverse events with a >10% higher incidence in Japanese patients (Cohort 3 of Study BCM-001) than in non-Japanese patients (either or both of Cohort 1 of Study BCM-001 and the entire population in Study 017001 [DLBCL cohort]).

Table 32. Summary of safety in Japanese and non-Japanese patients, and adverse events with a >10% higher incidence in Japanese than in non-Japanese patients (Study 017001 [DLBCL cohort], Study BCM-001)

PT (MedDRA ver. 21.0)	Number of patients (%)		
	Japanese patients (Cohort 3 of Study BCM-001) (n = 10)	Non-Japanese patients (Cohort 1 of Study BCM-001) (n = 36)	Non-Japanese patients (entire population of Study 017001 [DLBCL cohort]) (n = 269)
All adverse events	10 (100)	36 (100)	267 (99.3)
Grade ≥ 3 adverse events	9 (90.0)	34 (94.4)	213 (79.2)
Serious adverse events	2 (20.0)	18 (50.0)	122 (45.4)
Adverse events resulting in death	1 (10.0)	2 (5.6)	7 (2.6)
Adverse events with a >10% higher incidence			
Leukopenia	9 (90.0)	8 (22.2)	44 (16.4)
Neutropenia	9 (90.0)	32 (88.9)	169 (62.8)
Thrombocytopenia	9 (90.0)	16 (44.4)	84 (31.2)
Anaemia	8 (80.0)	18 (50.0)	129 (48.0)
Cytokine release syndrome	5 (50.0)	14 (38.9)	113 (42.0)
Fatigue	4 (40.0)	2 (5.6)	119 (44.2)
Hypofibrinogenaemia	4 (40.0)	1 (2.8)	3 (1.1)
Allergic transfusion reaction	2 (20.0)	0	0
Grade ≥3 adverse events with a >10% higher incidence			
Neutropenia	9 (90.0)	30 (83.3)	161 (59.9)
Leukopenia	8 (80.0)	8 (22.2)	39 (14.5)
Anaemia	7 (70.0)	11 (30.6)	101 (37.5)
Thrombocytopenia	7 (70.0)	9 (25.0)	72 (26.8)
Hypofibrinogenaemia	2 (20.0)	1 (2.8)	2 (0.7)

PMDA's view:

Serious adverse events were observed at high incidences in Studies 017001 and BCM-001. After Breyanzi infusion, patients should be monitored extremely carefully, and adverse event, if any, should be resolved by a multidisciplinary approach. Given that adverse events such as leukopenia were observed at higher incidences in Japanese patients than in non-Japanese patients, more careful adverse event management is required in Japanese patients, although the limited use experience with Breyanzi

in Japanese patients precludes strict comparison of the safety of Breyanzi between Japanese and non-Japanese patients.

6.R.3.2 Safety profile of Breyanzi by event

PMDA reviewed the safety profile of Breyanzi as follows based on the data from Studies 017001 and BCM-001 with a focus on frequently observed events and serious events.

6.R.3.2.1 CRS

The applicant's explanation about (a) the incidence of CRS in the clinical studies, (b) risk factors of onset and aggravation of CRS, and (c) the management of CRS following Breyanzi infusion:

(a) Incidence of CRS in the clinical studies

Adverse events falling into the preferred term (PT) of "Cytokine release syndrome" in the Medical Dictionary for Regulatory Activities Japanese version (MedDRA) were investigated.

In Studies 017001 and BCM-001, the grade definition of CRS based on Lee's criteria (*Blood*. 2014;124:188-95) in Table 33 was used.

Table 33. Grade definition of CRS

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

Tables 34 and 35 show the incidences of CRS-related events in Studies 017001 and BCM-001.

Table 34. Incidence of CRS (Studies 017001 and BCM-001)

	Number of patients (%)		
	Study 017001 (DLBCL cohort) (n = 269)	Study 017001 (MCL cohort) (n = 17)	Study BCM-001 (n = 46)
All adverse events	113 (42.0)	9 (52.9)	19 (41.3)
Grade ≥ 3 adverse events	6 (2.2)	1 (5.9)	2 (4.3)
Serious adverse events	44 (16.4)	4 (23.5)	7 (15.2)
Adverse events resulting in death	0	0	0

Table 35. List of patients with Grade ≥3 CRS (Studies 017001 and BCM-001)

Age	Sex	Grade	Seriousness	Causal relationship	Time to onset (days)	Duration (days)	Outcome	Treated or untreated with Tocilizumab/Number of doses
Study 017001 (DLBCL cohort)								
7	Male	3	Serious	Yes	9	1	Improved	Treated/1
		3	Serious	Yes	11	1	Improved	
6	Male	4	Serious	Yes	4	-	Not resolved	Treated/2
2	Male	3	Serious	Yes	8	2	Not resolved	Treated/2
		4	Serious	Yes	9	8	Resolved	
1	Male	3	Non-serious	Yes	12	1	Improved	Treated/1
4	Male	3	Serious	Yes	3	6	Resolved	Treated/2
6	Male	3	Serious	Yes	5	2	Improved	Treated/1
Study 017001 (MCL cohort)								
7	Male	4	Serious	Yes	11	-	Not resolved	Treated/2
Study BCM-001								
6	Male	4	Serious	Yes	7	-	Not resolved	Treated/2
5	Male	4	Serious	Yes	5	7	Resolved	Treated/4

No CRS resulting in death has been reported as of now.

The median number of days (range) from the start of Breyanzi treatment to the first onset of CRS was 5.0 days (1-14 days) in Study 017001 (DLBCL cohort), 7.0 days (2-10 days) in Study 017001 (MCL cohort), and 4.0 days (2-14 days) in Study BCM-001.

(b) Risk factors of onset and aggravation of CRS

CRS is defined as a systemic inflammatory reaction caused by inflammatory cytokines (e.g., IFN-γ) released by activated T cells. High tumor volume and high inflammatory cytokine level at baseline are related to increased incidence of CRS (*Blood.* 2014;124:188-95 and *Bone Marrow Transplant.* 2019;54:780–4). Prognostic factors for CRS were investigated based on the data of clinical studies on Breyanzi. Results showed that the incidence of CRS was higher in the subgroup with a high tumor volume (a high value in the sum of the product of the greatest diameters or in LDH in the lesion before LD chemotherapy), the subgroup with high CRP, and the subgroup that underwent anticancer therapies for disease control before LD chemotherapy.

(c) Management of CRS

Table 36 shows the outline of the CRS management algorithm in Studies 017001 and BCM-001.

Table 36. Outline of CRS management algorithm (Studies 017001 and BCM-001)

	Management method
After Breyanzi administration	• Monitor for CRS symptoms (pyrexia, unstable hemodynamics, hypoxia) according to the protocol and perform neurological evaluation. • Monitor serum CRP, ferritin, and coagulation parameters. • Consider hospitalization for close monitoring.
First-line treatment (a) Pyrexia of ≥38.5°C or any Grade ≥2 CRS sign or symptom within 72 hours after Breyanzi infusion (b) Pyrexia of ≥38°C after 72 hours after Breyanzi infusion, with CRS clinically progressed or rapidly aggravated after symptomatic treatment, etc.	• Grade 1 CRS: (a) Consider intravenous administration of tocilizumab 8 mg/kg (alone or in combination with dexamethasone 10 mg 24 hours apart). (b) Provide symptomatic treatment. • Grade 2 CRS: (a) Administer tocilizumab 8 mg/kg and dexamethasone 10 mg (12-24 hours apart) intravenously. (b) Administer tocilizumab 8 mg/kg (alone or in combination with dexamethasone 10 mg 12-24 hours apart) intravenously. • Grade 3 CRS: Administer tocilizumab 8 mg/kg and dexamethasone 10 mg (12 hours apart) intravenously. • Grade 4 CRS: Administer tocilizumab 8 mg/kg and dexamethasone 20 mg (6 hours apart) intravenously.
	• For CRS unimproved or rapidly progressed within 24 hours of the first line treatment, start the second line treatment.
Second-line treatment	• Administer the second dose of tocilizumab 8 mg/kg and dexamethasone 20 mg (6-12 hours apart) intravenously. • Search for other causes of clinical aggravation (e.g., sepsis, adrenal insufficiency).
	• For CRS unimproved or rapidly progressed within 24 hours of the second-line treatment, start the third-line treatment.
Third-line treatment	• Administer methylprednisolone 2 mg/kg, followed by a total of 2 mg/kg in 4 divided doses per day (to be tapered off within 7 days). • Consider using other anti-IL-6 drugs.
	• For CRS persisting even after the above treatments, start the fourth-line treatment.
Fourth-line treatment	• Consider anti-T cell therapy with cyclophosphamide 1.5 g/m^2, etc.
Other considerations*	• Dexamethasone, once started, should be administered ≥3 times or until the disappearance of CRS and related neurological symptoms. • Grade 1 CRS: Consider convulsive seizure prevention (e.g., administration of levetiracetam). • Grade 2 CRS: Frequently monitor the patient under the hospitalized conditions until pyrexia and symptoms resolve. Perform neurological evaluation and symptomatic therapies (oxygen supplementation, intravenous transfusion, and aggressive electrolyte replenishment, antipyretics, and low-dose vasopressor). Start convulsive seizure prevention (e.g., administration of levetiracetam) and, if neurotoxicity is observed, consider brain wave monitoring. • Grade ≥3 CRS: Perform monitoring, symptomatic treatment, hemodynamic and respiratory assistance, and neurological evaluation at ICU. Start convulsive seizure prevention (e.g., administration of levetiracetam) and, if neurotoxicity is observed, consider brain wave monitoring. • (Study BCM-001 only) Grade ≥3 CRS: In order to exclude the possibility of hemophagocytic lymphohistiocytosis, monitor the level of ferritin, triglycerides, and fibrinogen, and investigate the possibility of complication by infection, an inducing factor, by bone-marrow puncture.

PMDA's view:

In the clinical studies, CRS occurred frequently after Breyanzi administration with some serious cases. In addition, CRS occurred no more than around 2 days after the start of Breyanzi administration. Given these, Breyanzi treatment requires hospitalization and close monitoring particularly during the early post-treatment phase. The occurrence of CRS and the method for CRS management practiced in the clinical studies should be appropriately communicated to healthcare professionals via the package insert to call attention. Furthermore, Breyanzi must be administered by a physician with sufficient knowledge and experience in systemic control on hematopoietic malignancy and critical conditions such as CRS, and at a medical institution with an intensive care unit (ICU), etc. for immediate systemic control in emergency. This should also be advised via the package insert, etc.

6.R.3.2.2 Hemophagocytic lymphohistiocytosis

The applicant's explanation about hemophagocytic lymphohistiocytosis caused by Breyanzi administration:

Adverse events falling under the MedDRA PT of "histiocytosis haematophagic" are listed in Table 37.

Table 37. List of patients with hemophagocytic lymphohistiocytosis

Study	Age	Sex	PT (MedDRA ver. 21.0)	Grade	Serious/ non-serious	Time to onset (days)	Occurrence of CRS	Causal relationship to Breyanzi
BCM-001	6[redacted]	Man	Histiocytosis haematophagic	3	Serious	8	Occurred	Related
			Histiocytosis haematophagic	4	Serious	15	Occurred	Related
	5[redacted]	Man	Histiocytosis haematophagic	4	Serious	9	Occurred	Related

Hemophagocytic lymphohistiocytosis is related to severe or life-threatening CRS. It is observed also with approved anti-CD19 CAR T cell therapy, and is considered to be caused by excessive activation of CD8-positive T cells *(Best Pract Res Clin Rheumatol*. 2014;28:277–92). Both 2 patients who experienced hemophagocytic lymphohistiocytosis in the clinical studies of Breyanzi had Grade 3 or 4 CRS.

PMDA's view:

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

6.R.3.2.3 Nerve disorder

The applicant's explanation about nerve disorder associated with Breyanzi:

Adverse events falling under the MedDRA SOC of "Nervous system disorders" or "Psychiatric disorders" were counted as nerve disorders. Tables 38, 39, and 40 show the incidences of nerve disorder in Studies 017001 and BCM-001.

Table 38. Incidence of nerve disorder (Studies 017001 and BCM-001)

	Number of patients (%)		
	Study 017001 (DLBCL cohort) (n = 269)	Study 017001 (MCL cohort) (n = 17)	Study BCM-001 (n = 46)
All adverse events	200 (74.3)	10 (58.8)	23 (50.0)
Grade ≥ 3 adverse events	40 (14.9)	3 (17.6)	5 (10.9)
Serious adverse events	53 (19.7)	3 (17.6)	7 (15.2)
Adverse events resulting in death	1 (0.4)	0	0

Table 39. Incidences of nerve disorder reported by ≥5% of patients (Study 017001 [DLBCL cohort])

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) N = 269	
	All Grades	Grade ≥3
Nervous system disorders		
Headache	80 (29.7)	3 (1.1)
Dizziness	60 (22.3)	1 (0.4)
Tremor	41 (15.2)	0
Aphasia	22 (8.2)	3 (1.1)
Encephalopathy	19 (7.1)	12 (4.5)
Lethargy	15 (5.6)	0
Psychiatric disorders		
Confusional state	39 (14.5)	2 (0.7)
Insomnia	36 (13.4)	1 (0.4)
Anxiety	27 (10.0)	0

Table 40. Incidences of nerve disorder reported by ≥2 patients (Study BCM-001)

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) N = 46	
	All Grades	Grade ≥3
Nervous system disorders		
Headache	7 (15.2)	0
Tremor	5 (10.9)	1 (2.2)
Aphasia	4 (8.7)	3 (6.5)
Dizziness	2 (4.3)	0
Memory impairment	2 (4.3)	1 (2.2)
Somnolence	2 (4.3)	0
Psychiatric disorders		
Confusional state	7 (15.2)	3 (6.5)
Delirium	3 (6.5)	2 (4.3)
Depression	2 (4.3)	0
Disorientation	2 (4.3)	1 (2.2)

In Study 017001 (MCL cohort), events observed in ≥2 patients were headache and insomnia in 4 patients each, anxiety in 3 patients, and depression in 2 patients.

Death due to nerve disorder occurred in 1 patient (leukoencephalopathy) in Study 017001 (DLBCL cohort), but its causal relationship to Breyanzi was ruled out.

Table 41 shows the characteristics of the patients who experienced Grade ≥3 nerve disorder in Studies 017001 and BCM-001.

Table 41. List of patients experiencing Grade ≥3 nerve disorder

Age	Sex	PT (MedDRA ver. 21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to Breyanzi	Outcome
Study 017001 (DLBCL cohort)								
7[redacted]	Male	Encephalopathy	3	Non-serious	6	5	Related	Resolved
		Encephalopathy	4	Serious	11	-	Related	Not resolved
7[redacted]	Male	Confusional state	3	Serious	8	5	Related	Improved
6[redacted]	Male	Delirium	3	Non-serious	4	-	Related	Not resolved
7[redacted]	Male	Insomnia	3	Non-serious	23	34	Related	Improved
5[redacted]	Male	Mental status changes	3	Serious	9	15	Related	Improved
3[redacted]	Male	Aphasia	3	Serious	15	2	Related	Resolved
4[redacted]	Female	Agitation	3	Non-serious	7	3	Related	Resolved
		Dysarthria	3	Non-serious	7	3	Related	Resolved
		Encephalopathy	3	Serious	7	9	Related	Resolved
1[redacted]	Male	Agitation	3	Serious	34	3	Related	Resolved
		Mental status changes	3	Serious	34	3	Related	Resolved
6[redacted]	Female	Syncope	3	Serious	64	4	Not related	Resolved
3[redacted]	Female	Seizure	4	Serious	14	15	Related	Resolved
4[redacted]	Male	Encephalopathy	3	Serious	44	5	Related	Improved
7[redacted]	Male	Encephalopathy	3	Serious	11	4	Related	Improved
8[redacted]	Male	Encephalopathy	3	Serious	8	6	Related	Improved
		Agitation	3	Serious	10	2	Related	Resolved
		Agitation	3	Serious	21	2	Related	Resolved
		Somnolence	3	Serious	20	-	Related	Not resolved
5[redacted]	Male	Encephalopathy	4	Serious	8	-	Related	Not resolved
5[redacted]	Male	Headache	3	Non-serious	3	4	Related	Improved
6[redacted]	Female	Depression	3	Serious	42	83	Not related	Resolved
7[redacted]	Male	Leukoencephalopathy	3	Serious	51	16	Not related	Not resolved
		Leukoencephalopathy	4	Serious	66	6	Not related	Not resolved
		Leukoencephalopathy	5	Serious	71	1	Not related	Dead
		Syncope	3	Serious	34	2	Not related	Resolved
6[redacted]	Female	Aphasia	3	Serious	14	2	Related	Resolved
		Aphasia	3	Non-serious	21	2	Related	Resolved
		Encephalopathy	3	Serious	14	18	Related	Improved
		Somnolence	3	Non-serious	15	6	Related	Resolved
		Somnolence	3	Non-serious	27	3	Related	Improved
		Somnolence	3	Non-serious	30	-	Related	Not resolved
4[redacted]	Male	Encephalopathy	3	Serious	12	4	Related	Improved
		Encephalopathy	4	Serious	16	2	Related	Improved
6[redacted]	Female	Leukoencephalopathy	4	Serious	30	49	Not related	Improved
		Leukoencephalopathy	3	Serious	78	71	Not related	Improved
2[redacted]	Male	Depressed level of consciousness	3	Non-serious	23	3	Related	Improved
		Encephalopathy	3	Non-serious	17	11	Related	Improved
		Seizure	3	Serious	16	2	Related	Resolved
7[redacted]	Female	Syncope	3	Non-serious	2	4	Related	Resolved
5[redacted]	Male	Headache	3	Non-serious	4	3	Not related	Improved
7[redacted]	Male	Confusional state	3	Non-serious	10	5	Related	Improved
6[redacted]	Female	Diplegia	3	Serious	14	-	Not related	Not resolved
6[redacted]	Female	Depressed level of consciousness	3	Serious	6	8	Related	Improved
1[redacted]	Male	Facial paralysis	3	Serious	12	2	Related	Resolved
		Hallucination	4	Serious	33	2	Not related	Resolved
		Headache	3	Non-serious	12	3	Related	Resolved
7[redacted]	Male	Syncope	3	Serious	1	2	Not related	Resolved
		Syncope	3	Serious	83	3	Not related	Resolved
7[redacted]	Female	Encephalopathy	3	Serious	2	9	Related	Resolved
		Dysarthria	3	Non-serious	3	-	Not related	Not resolved
6[redacted]	Male	Mental status changes	3	Serious	26	-	Not related	Not resolved
5[redacted]	Male	Dysarthria	3	Non-serious	18	2	Related	Improved
7[redacted]	Female	Syncope	3	Non-serious	32	1	Not related	Resolved
6[redacted]	Female	Syncope	3	Serious	12	2	Not related	Resolved
6[redacted]	Male	Dizziness	3	Non-serious	17	19	Related	Improved
6[redacted]	Male	Agitation	3	Serious	10	3	Related	Resolved
		Aphasia	3	Serious	10	3	Related	Resolved
		Disorientation	3	Serious	10	3	Related	Resolved
6[redacted]	Female	Encephalopathy	3	Serious	8	5	Related	Improved
6[redacted]	Male	Encephalopathy	3	Non-serious	18	-	Not related	Not resolved
5[redacted]	Female	Nerve root compression	3	Non-serious	6	4	Not related	Improved
7[redacted]	Female	Mental status changes	3	Serious	9	3	Related	Resolved
6[redacted]	Male	Ataxia	3	Non-serious	5	2	Related	Improved
		Mental status changes	3	Non-serious	5	2	Related	Resolved

Age	Sex	PT (MedDRA ver. 21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to Breyanzi	Outcome
Study 017001 (MCL cohort)								
5[redacted]	Male	Syncope	3	Non-serious	9	1	Not related	Resolved
		Syncope	3	Serious	22	1	Related	Resolved
6[redacted]	Female	Mental status changes	3	Serious	9	3	Related	Resolved
6[redacted]	Female	Encephalopathy	3	Serious	8	2	Related	Resolved
Study BCM-001								
5[redacted]	Female	Aphasia	3	Serious	8	4	Related	Resolved
		Tremor	3	Serious	8	4	Related	Resolved
6[redacted]	Male	Confusional state	3	Serious	6	2	Related	Not resolved
		Depressed level of consciousness	3	Serious	6	2	Related	Not resolved
		Depressed level of consciousness	4	Serious	7	-	Related	Not resolved
		Stupor	3	Serious	6	2	Related	Not resolved
6[redacted]	Female	Aphasia	3	Serious	7	13	Related	Resolved
		Bradyphrenia	3	Serious	7	13	Related	Resolved
5[redacted]	Male	Aphasia	3	Serious	9	2	Related	Resolved
		Confusional state	3	Serious	9	9	Related	Resolved
		Delirium	4	Serious	18	-	Related	Not resolved
		Disorientation	3	Serious	9	9	Related	Resolved
		Paranoia	4	Non-serious	30	5	Related	Resolved (with sequelae)
		Seizure	3	Serious	13	2	Related	Resolved
7[redacted]	Male	Confusional state	3	Serious	16	4	Related	Resolved
		Delirium	3	Serious	18	3	Related	Resolved
		Memory impairment	3	Serious	17	3	Related	Resolved

The median number of days (range) from the administration of Breyanzi to the first onset of nerve disorder was 5.0 days (1-90 days) in Study 017001 (DLBCL cohort), 4.0 days (1-15 days) in Study 017001 (MCL cohort), and 9.0 days (1-81 days) in Study BCM-001.

PMDA's view:

Because the incidence of Breyanzi-associated nerve disorder was high with some fatal or serious cases, caution should be exercised against nerve disorder in the use of Breyanzi, and the patient should be carefully monitored after Breyanzi infusion. Accordingly, the occurrence of nerve disorder in the clinical studies and their breakdown should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention.

6.R.3.2.4 Infection

The applicant's explanation about infection associated with Breyanzi:

Adverse events falling under the MedDRA SOC of "Infections and infestations" were counted as infections, and are listed in Tables 42 and 43.

Table 42. Incidences of infection reported by ≥2% of patients (Study 017001 [DLBCL cohort])

PT (MedDRA ver. 21.0)	Number of patients (%) N = 269	
	All Grades	Grade ≥3
Infection	110 (40.9)	33 (12.3)
Pneumonia	16 (5.9)	8 (3.0)
Upper respiratory tract infection	12 (4.5)	1 (0.4)
Candida infection	11 (4.1)	0
Sinusitis	10 (3.7)	1 (0.4)
Clostridium difficile infection	9 (3.3)	1 (0.4)
Rhinovirus infection	9 (3.3)	0
Urinary tract infection	9 (3.3)	4 (1.5)
Oral candidiasis	6 (2.2)	0

Table 43. Incidences of infection reported by ≥2 patients (Study BCM-001)

PT (MedDRA ver. 21.0)	Number of patients (%) N = 46	
	All Grades	Grade ≥3
Infection	17 (37.0)	7 (15.2)
Candida sepsis	2 (4.3)	2 (4.3)
Cellulitis	2 (4.3)	1 (2.2)
Lung infection	2 (4.3)	1 (2.2)
Pneumonia	2 (4.3)	2 (4.3)

In Study 017001 (MCL cohort), infection was observed in 7 of 17 patients (41.2%), and a Grade ≥3 event was observed in 1 patient (periorbital cellulitis).

Infection resulted in death in 2 patients (septic shock and progressive multifocal leukoencephalopathy [PML]) in Study 017001 and 1 patient (Candida sepsis) in Study BCM-001.

Serious infections observed were pneumonia in 8 patients, sepsis in 4 patients; Clostridium difficile infection and septic shock in 3 patients each; Streptococcal bacteraemia in 2 patients; appendicitis, bacterial sepsis, Clostridium difficile colitis, conjunctivitis, cytomegalovirus (CMV) infection, CMV viraemia, Enterococcal bacteraemia, enterovirus infection, influenza, parainfluenza virus infection, progressive multifocal leukoencephalopathy, Staphylococcal bacteraemia, systemic candida, upper respiratory tract infection, and urinary tract infection in 1 patient each in Study 017001 (DLBCL cohort); and diverticulitis and periorbital cellulitis in 1 patient each in Study 017001 (MCL cohort). Serious infections observed in Study BCM-001 were Candida sepsis in 2 patients; cellulitis, Clostridium colitis, device-related sepsis, pneumonia, and Staphylococcal sepsis in 1 patient each.

Table 44 shows patients with human herpes virus (HHV) reactivation in Studies 017001 and BCM-001. Reactivation of hepatitis virus, aggravation of hepatitis, or aggravation of HIV infection was not observed.

Table 44. List of patients with HHV reactivation (Studies 017001 and BCM-001)

Age	Sex	PT (MedDRA ver. 21.0)	Grade	Seriousness	Time to onset (days)	Causal relationship to Breyanzi	Outcome
Study 017001 (DLBCL cohort)							
6	Female	CMV infection	2	Non-serious	22	Not related	Resolved
4	Male	Herpes zoster	1	Non-serious	42	Not related	Resolved
6	Male	Herpes zoster	2	Non-serious	64	Not related	Resolved
8	Male	Herpes simplex	2	Non-serious	10	Not related	Not resolved
5	Male	CMV viraemia	2	Serious	1	Not related	Resolved
5	Male	CMV infection	2	Non-serious	35	Not related	Resolved
6	Male	CMV viraemia	2	Non-serious	2	Related	Resolved
		Herpes simplex	2	Non-serious	2	Related	Resolved
		HHV6 infection	2	Non-serious	2	Related	Resolved
6	Female	CMV infection	3	Serious	24	Not related	Resolved
5	Male	CMV infection	1	Non-serious	35	Not related	Resolved
6	Female	Herpes zoster	2	Non-serious	144	Not related	Resolved
Study BCM-001							
5	Male	Varicella zoster virus infection	2	Non-serious	46	Not related	Resolved

PMDA's view:

Given the fatal infection, Grade ≥3 infection, and serious infection observed in association with Breyanzi, caution should be exercised against infection associated with Breyanzi. Accordingly, the occurrence of infection in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention. Although reactivation of hepatitis virus, aggravated hepatitis, or aggravated HIV infection was not observed in the clinical studies, patients with a high risk of reactivation or aggravation were excluded from the studies. The target population for Breyanzi treatment in the clinical studies should be appropriately communicated to healthcare professionals to call attention.

6.R.3.2.5 Bone marrow depression

The applicant's explanation about bone marrow depression associated with Breyanzi:

Events related to bone marrow depression were classified into erythropenia, neutropenia, thrombocytopenia, and pancytopenia as show in Table 45. Table 46 shows the incidences of these classified events.

Table 45. List of events included in bone marrow depression

Classification	MedDRA PT (MedDRA/J version 21.0)
Erythropenia	Anaemia, anaemia macrocytic, anaemia megaloblastic, haematocrit decreased, haemoglobin decreased, hyperchromic anaemia, hypochromic anaemia, leukoerythroblastic anaemia, microcytic anaemia, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia, red blood cell count decreased, sideroblastic anaemia
Neutropenia	Agranulocytosis, autoimmune neutropenia, band neutrophil count decreased, band neutrophil percentage decreased, benign ethnic neutropenia, cyclic neutropenia, FN, Felty's syndrome, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic colitis, neutropenic sepsis, neutropenic infection, neutrophil count decreased
Thrombocytopenia	Acquired amegakaryocytic thrombocytopenia, megakaryocytes decreased, platelet count decreased, platelet maturation arrest, platelet production decreased, platelet toxicity, thrombocytopenia
Pancytopenia	Aplastic anaemia, autoimmune aplastic anaemia, autoimmune pancytopenia, bicytopenia, bone marrow failure, febrile bone marrow aplasia, full blood count decreased, pancytopenia, Shwachman-Diamond syndrome

Table 46. Incidences of bone marrow depression (Studies 017001 and BCM-001)

PT (MedDRA ver. 21.0)	Number of patients (%)					
	Study 017001 (DLBCL cohort) (n = 269)		Study 017001 (MCL cohort) (n = 17)		Study BCM-001 (n = 46)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Bone marrow depression	206 (76.6)	194 (72.1)	12 (70.6)	10 (58.8)	44 (95.7)	41 (89.1)
Neutropenia	169 (62.8)	161 (59.9)	7 (41.2)	6 (35.3)	41 (89.1)	39 (84.8)
Anaemia	129 (48.0)	101 (37.5)	9 (52.9)	7 (41.2)	26 (56.5)	18 (39.1)
Thrombocytopenia	84 (31.2)	72 (26.8)	6 (35.3)	6 (35.3)	25 (54.3)	16 (34.8)
FN	25 (9.3)	24 (8.9)	3 (17.6)	2 (11.8)	8 (17.4)	8 (17.4)
Pancytopenia	3 (1.1)	3 (1.1)	0	0	1 (2.2)	1 (2.2)
Bone marrow failure	1 (0.4)	1 (0.4)	0	0	0	0

There was no bone marrow depression resulting in death.

Serious bone marrow depression was observed in 25 of 269 patients (9.3%) in Study 017001 (DLBCL cohort), i.e., neutropenia in 11 patients, febrile neutropenia (FN) and thrombocytopenia in 10 patients each, anaemia in 5 patients, pancytopenia and bone marrow failure in 1 patient each. In Study 017001 (MCL cohort), serious bone marrow depression was observed in 2 of 17 patients (11.8%), and they

were anaemia, thrombocytopenia, and FN in 1 patient each. In Study BCM-001, serious bone marrow depression was observed in 5 of 46 patients (10.9%), and they were FN in 4 patients, and neutrophil count decreased, anaemia, and thrombocytopenia in 1 patient each.

Table 47 shows the time of onset, duration, and recovery period of bone marrow depression.

Table 47. Time of onset, duration, and recovery period of bone marrow depression

Classification	Study	Median time to onset (after administration of Breyanzi) (range) (days)	Median duration (range) (days)	Median time to resolution (range) (days)
Erythropenia	017001[a)]	6.0 (1-55)	8.0 (1-272)	14.5 (2-280)
	BCM-001	5.5 (1-35)	17.0 (1-198)	28.0 (6-221)
Neutropenia	017001[a)]	4.0 (1-72)	8.0 (1-542)	12.0 (1-552)
	BCM-001	4.0 (1-83)	14.0 (1-161)	16.0 (2-163)
Thrombocytopenia	017001[a)]	9.0 (1-47)	21.0 (1-259)	35.5 (4-260)
	BCM-001	14.0 (1-37)	33.0 (6-315)	50.5 (7-331)
Pancytopenia	017001[a)]	19.0 (6-31)	16.0 (1)	39.0 (1)
	BCM-001	9.0 (1)	-	-

a) DLBCL cohort

PMDA's view:

Caution should be exercised against Breyanzi-associated bone marrow depression because clinical study participants experienced serious bone marrow depression events. Accordingly, the occurrence and duration, etc. of bone marrow depression in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. In addition, the following cautionary advice should be appropriately provided to healthcare professionals via the package insert, etc: Blood tests should be performed regularly after Breyanzi infusion, and appropriate measures should be taken for bone marrow depression, once detected.

6.R.3.2.6 Hypersensitivity

The applicant's explanation about hypersensitivity associated with Breyanzi:

Adverse events falling under the standardised MedDRA queries (SMQ) (narrow) of "Hypersensitivity" are listed in Table 48. The protocols of the clinical studies on Breyanzi stipulated that subjects must receive premedication with acetaminophen and diphenhydramine hydrochloride (or other H1 anti-histaminic agent) 30 to 60 minutes prior to Breyanzi infusion.

Table 48. Incidences of hypersensitivity observed in ≥2 patients in either study (Studies 017001 and BCM-001)

PT (MedDRA ver. 21.0)	Number of patients (%)					
	Study 017001 (DLBCL cohort) n = 269		Study 017001 (MCL cohort) n = 17		Study BCM-001 n = 46	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypersensitivity	39 (14.5)	1 (0.4)	4 (23.5)	1 (5.9)	10 (21.7)	1 (2.2)
Rash	13 (4.8)	0	1 (5.9)	0	2 (4.3)	0
Infusion related reaction	5 (1.9)	0	1 (5.9)	0	0	0
Rash maculo-papular	4 (1.5)	1 (0.4)	0	0	1 (2.2)	1 (2.2)
Hypersensitivity	3 (1.1)	0	0	0	0	0
Rash pruritic	2 (0.7)	0	0	0	1 (2.2)	0
Rash pustular	2 (0.7)	0	1 (5.9)	0	0	0
Scrotal oedema	2 (0.7)	0	0	0	0	0
Dermatitis acneiform	1 (0.4)		0	0	2 (4.3)	0
Allergic transfusion reaction	0	0	0	0	2 (4.3)	0

Table 49 shows characteristics of the patients who experienced Grade ≥3 hypersensitivity in Studies 017001 and BCM-001. Serious hypersensitivity was observed in 1 patient in Study 017001 (MCL cohort). No patients died of hypersensitivity.

Table 49. List of patients with serious or Grade ≥3 hypersensitivity

Age	Sex	PT (MedDRA ver. 21.0)	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to Breyanzi	Outcome
Study 017001 (DLBCL cohort)								
5	Women	Rash maculo-papular	3	Non-serious	22	6	Not related	Resolved
Study 017001 (MCL cohort)								
7	Man	Shock	4	Serious	10	-	Related	Not resolved
Study BCM-001								
6	Woman	Rash maculo-papular	3	Non-serious	15	-	Related	Not resolved

The median number of days (range) from Breyanzi infusion to the first onset of hypersensitivity was 6.0 days (1-72 days) in Study 017001 (DLBCL cohort), 5.5 days (4-10 days) in Study 017001 (MCL cohort), and 11.5 days (2-41 days) in Study BCM-001.

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

6.R.3.2.7 Hypogammaglobulinemia

The applicant's explanation about hypogammaglobulinemia associated with Breyanzi:
Adverse events falling under the MedDRA PTs of "Blood immunoglobulin A decreased," "Blood immunoglobulin D decreased," "Blood immunoglobulin E decreased," "Blood immunoglobulin G decreased," "Blood immunoglobulin M decreased," "Hypogammaglobulinaemia," "Immunoglobulins decreased," "Selective IgA immunodeficiency," "Selective IgG subclass deficiency," and "Selective IgM immunodeficiency" were counted as Hypogammaglobulinemia, and are listed in Table 50. In Study 017001 (MCL cohort), hypogammaglobulinemia was observed in 2 of 17 patients (11.8%).

Table 50. Incidence of hypogammaglobulinemia or agammaglobulinemia (Studies 017001 [DLBCL cohort] and BCM-001)

PT (MedDRA Version 21.0)	Number of patients (%)			
	Study 017001 (DLBCL cohort) n = 269		Study BCM-001 n = 46	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypo- or a-gammaglobulinaemia	37 (13.8)	0	7 (15.2)	0
Hypogammaglobulinaemia	37 (13.8)	0	6 (13.0)	0
Immunoglobulins decreased	0	0	1 (2.2)	0

In Studies 017001 and BCM-001, neither fatal nor serious or Grade ≥3 hypogammaglobulinemia occurred associated with Breyanzi.

The median number of days (range) from Breyanzi infusion to the first onset of

hypogammaglobulinemia was 24.0 days (1-86 days) in Study 017001 (DLBCL cohort), 59.0 days (34-84 days) in Study 017001 (MCL cohort), and 22.0 days (7-300 days) in Study BCM-001.

PMDA's view:
Although Grade ≥3 hypogammaglobulinemia did not occur in patients receiving Breyanzi in the clinical studies, hypogammaglobulinemia associated with Breyanzi infusion deserves caution, because hypogammaglobulinemia is an attention-calling event of tisagenlecleucel, an anti-CD19 CAR T cell formulation with a Breyanzi-like mechanism of action, and anti-CD19 CAR T cell administration may cause B cell depletion in the body. Accordingly, the occurrence of hypogammaglobulinemia in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention so that appropriate measures are taken in case of hypogammaglobulinemia.

6.R.3.2.8 TLS

The applicant's explanation about TLS associated with Breyanzi:
Adverse events falling under the MedDRA PT of "Tumour lysis syndrome" were counted as TLS. Table 51 shows the characteristics of the patients who had TLS after Breyanzi infusion. No TLS occurred in Study BCM-001.

Table 51. List of patients with TLS (Study 017001)

	Age	Sex	Grade	Seriousness	Time to onset (days)	Duration (days)	Causal relationship to Breyanzi	Outcome
DLBCL cohort	2[redacted]	Man	3	Non-serious	1	5	Not related	Resolved
	5[redacted]	Man	3	Non-serious	1	30	Related	Resolved
MCL cohort	7[redacted]	Man	4	Serious	10	3	Related	Not resolved
			5	Serious	12	1	Related	Dead

PMDA's view:
In Study 017001, TLS for which a causal relationship to Breyanzi could not be ruled out were reported by 2 patients, and 1 of them died. Also, TLS is an attention-calling event of tisagenlecleucel, an anti-CD19 CAR T cell formulation with a Breyanzi-like mechanism of action. Accordingly, caution should be exercised against TLS in patients receiving Breyanzi. The occurrence of TLS in the clinical studies should be appropriately communicated to healthcare professionals via the package insert, etc. to call attention so that appropriate measures are taken in case of TLS.

6.R.3.2.9 Others

6.R.3.2.9.1 Secondary malignant tumor

The applicant's explanation about secondary malignant tumor:
Adverse events falling under the MedDRA SMQ of "Premalignant disorders" or "Malignancies" were counted as secondary malignant tumor (including myelodysplastic syndrome). Table 52 shows a list of patients who experienced secondary malignant tumor that were assessed later based on the medical review[27)] of the assessment committee.

[27)] The medical review-based selection of adverse events excluded events that reflected baseline status before Breyanzi infusion unless showing progression from baseline after infusion.

Table 52. List of patients with serious or Grade ≥3 secondary malignant tumor

Age	Sex	PT (MedDRA ver. 21.0)	Grade	Serious/ non-serious	Time to onset (days)	Causal relationship to Breyanzi	Outcome
Study 017001 (DLBCL cohort)							
7	Women	Squamous cell carcinoma of lung	2	Serious	546	Not related	Resolved
7	Man	Neoplasm of appendix	3	Serious	271	Not related	Resolved
5	Man	Myelodysplastic syndrome	4	Serious	490	Related	Not resolved
5	Man	Squamous cell carcinoma	2	Serious	Approx. 450	Not related	Resolved
5	Man	Bladder transitional cell carcinoma	2	Serious	601	Not related	Resolved (with sequelae)
7	Man	Basal cell carcinoma	2	Serious	72	Not related	Resolved
6	Man	Basal cell carcinoma	1	Serious	175	Not related	Resolved
7	Man	Basal cell carcinoma	2	Serious	654	Not related	Resolved
6	Man	Myelodysplastic syndrome	4	Serious	732	Not related	Not resolved
7	Man	Basal cell carcinoma	3	Serious	95	Not related	Resolved
		Basal cell carcinoma	3	Serious	291	Not related	Resolved
		Basal cell carcinoma	3	Serious	459	Not related	Resolved
7	Woman	Myelodysplastic syndrome	3	Serious	106	Not related	Not resolved
7	Man	Basal cell carcinoma	3	Serious	115	Not related	Resolved
		Basal cell carcinoma	3	Serious	Approx. 150	Not related	Resolved
		Myelodysplastic syndrome	3	Serious	174	Not related	Not resolved
		Squamous cell carcinoma	3	Serious	115	Not related	Resolved
		Squamous cell carcinoma	3	Serious	265	Not related	Resolved
7	Man	Myelodysplastic syndrome	3	Serious	336	Not related	Not resolved
		Myelodysplastic syndrome	5	Serious	670	Not related	Dead
4	Man	Peripheral T-cell lymphoma unspecified	4	Serious	30	Related	Not resolved
7	Man	Acute myeloid leukaemia	4	Serious	101	Not related	Not resolved
6	Woman	Bowen's disease	2	Non-serious	1	Not related	Resolved
		Squamous cell carcinoma	2	Non-serious	1	Not related	Resolved
8	Man	Squamous cell carcinoma	2	Serious	354	Not related	Resolved
		Squamous cell carcinoma	2	Serious	441	Not related	Resolved
7	Woman	Basal cell carcinoma	2	Serious	191	Not related	Resolved
6	Woman	Myelodysplastic syndrome	4	Serious	70	Not related	Not resolved
6	Woman	Endometrial adenocarcinoma	2	Serious	68	Not related	Resolved
Study 017001 (MCL cohort)							
6	Woman	Lung adenocarcinoma	3	Serious	192	Not related	Resolved
6	Man	Squamous cell carcinoma	2	Serious	280	Not related	Resolved
Study BCM-001							
5	Woman	Lung adenocarcinoma	3	Serious	198	Not related	Not resolved

Among those who participated in Study 017001 and Study BCM-001, 2 patients had secondary malignant tumor for which a causal relationship to Breyanzi could not be ruled out in 2 patients in Study 017001 (peripheral T-cell lymphoma unspecified[28)] and myelodysplastic syndrome in 1 patient each). Results of tumor biopsy suggested that neither event corresponded to clonal CAR T cell proliferative disorder or malignant transformation induced by gene transfection. Myelodysplastic syndrome in 1 patient occurred approximately 1 year and 4 months after Breyanzi administration, suggesting that it was not a typical early treatment-induced myelodysplastic syndrome.

The types and frequency of the above-mentioned secondary malignant tumor were within the range of the secondary oncogenesis anticipated in the patient population receiving multiple prior medications that are known to be related to HSCT or secondary oncogenesis. The time of onset varied widely from 30 to 732 days after Breyanzi administration, showing no specific tendency and thereby suggesting no

[28)] CAR-positive cells were detected by qPCR in tumor specimens from 2 sites (chest and scalp) (256 copies/ug and 1189 copies/ug, respectively), but the cell number was <0.1% of the tumor specimen. CAR-positive cells were polyclonal; there were no cells that originated from the same CAR-positive cells in tumor cells of 2 sites. At tumor biopsy, CAR gene of Breyanzi administered was detected by qPCR (5087 copies/ug) and flow cytometry (7.7 cells/ul). Thus, although CAR-positive cells were detected from the tumor specimens, they were considered to be those present at the time of Breyanzi infusion, most likely ruling out the possibility of neoplastic proliferation of CAR-positive cells.

common mechanism of oncogenesis. Thus, there is no information at present that suggests any direct relationship between Breyanzi and secondary malignant tumor.

PMDA's view:
A relationship between secondary malignant tumor and primary disease or prior chemotherapy cannot be ruled out, and at present, the relationship between secondary malignant tumor and Breyanzi remains unclear. Some of the events, however, occurred shortly after Breyanzi infusion, and a causal relationship between Breyanzi and these events cannot be ruled out. Given this, caution should be exercised against secondary malignant tumor, and relevant information should be continuously collected in the post-marketing setting.

6.R.4 Clinical positioning and indication or performance

The proposed "Indication or Performance" of Breyanzi was "Relapsed or refractory large B-cell lymphoma."

The "Precautions Concerning Indications or Performance" section included the following statements: Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on knowledge from the "Clinical Studies" section, i.e., the tissue types and prior treatment, etc. of patients enrolled in the clinical studies.

PMDA's view:
Based on reviews in Sections "6.R.2 Efficacy," "6.R.3 Safety," and the review presented below, the "Clinical Studies" section of the package insert should elaborate the prior treatment of the patients included in Studies 017001 and BCM-001, and the "Indication or Performance" section should be specified as shown below:

Indications or Performance (Underline denotes additions.)
The following relapsed or refractory large B-cell lymphoma
- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed indolent non-Hodgkin lymphoma, high-grade large B-cell lymphoma

Relapsed or refractory follicular lymphoma

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen who meet any of the following criteria:
- Patients with large B-cell lymphoma other than transformed indolent non-Hodgkin lymphoma and patients with follicular lymphoma: ≥2 lines of prior chemotherapy in the first-onset patients or ≥1 line of prior post-relapse chemotherapy in relapsed patients, which failed to achieve complete response or resulted in another relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from follicular lymphoma: a total of ≥2 lines of prior chemotherapy including ≥1 after transformation, which failed to achieve complete response or resulted in relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from indolent B-cell non-Hodgkin lymphoma other than follicular lymphoma; ≥2 lines of prior chemotherapy after

transformation, which failed to achieve complete response or resulted in relapse

"Precautions Concerning Indications or Performance" (Underline denotes additions.)

- For follicular lymphoma, Breyanzi should be administered to patients with clinical condition of Grade 3B assessed by a well-experienced pathologist or by a test at an experienced testing facility.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on knowledge from the "Clinical Studies" section, i.e., the tissue types and prior treatment, etc. of the patients enrolled in the clinical studies.

6.R.4.1 Clinical positioning and target population of Breyanzi

The applicant's explanation about the clinical positioning and "Indication or Performance" of Breyanzi:

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas (NCCN Guidelines) (v.4.2020) recommends the administration of anti-CD19 CAR T cells to patients with large B-cell lymphoma (including DLBCL, PMBCL, TFL, and HGBCL) with ≥2 lines of prior chemotherapy (Category 2A[29)]).

The results of Studies 017001 and BCM-001 confirmed the efficacy and safety of Breyanzi in patients with relapsed or refractory large B-cell lymphoma with ≥2 lines of prior chemotherapy, indicating that Breyanzi is a novel treatment option for patients with relapsed or refractory large B-cell lymphoma with ≥2 lines of prior chemotherapy.

The "Indications or Performance" of Breyanzi was defined as large B-cell lymphoma by referring to the World Health Organization (WHO) Classification (fourth revision). However, in terms of Primary DLBCL of the CNS (PCNSL), one of the tissue types classified as large B-cell lymphoma in the WHO Classification (fourth revision), the Japanese and foreign clinical practice guidelines recommends a standard therapy that is largely different from that for other tissue types such as DLBCL, and patients with PCNSL was thus excluded from Studies 017001 and BCM-001 (Cohorts 1 and 3), leaving the efficacy and safety of Breyanzi in PCNSL unestablished. Accordingly, Breyanzi is not recommended for this patient population. Similarly, the efficacy and safety of Breyanzi have not been established for large B-cell lymphoma other than PCNSL according to the WHO Classification (fourth revision), which were not investigated in Study 017001 or BCM-001 (Cohorts 1 and 3). However, given its action mechanism, Breyanzi is expected to show efficacy against tissue types expressing CD19. Meanwhile, FL3B that was investigated in Studies 017001 and BCM-001 is not included in large B-cell lymphoma according to the WHO Classification (fourth revision). The tissue image of FL3B in a diffuse area is similar to that of DLBCL, and the NCCN Guidelines (v.4.2020), etc. recommend to follow the DLBCL treatment for FL3B. Therefore, FL3B is included in large B-cell lymphoma in "Indications or Performance."

"Indications or Performance" is proposed as per below, given that the results of Studies 017001 and BCM-001 indicated promising efficacy of Breyanzi in patients with relapsed or refractory large B-cell

[29)] The recommendation is based on a rather low level of evidence, but there is a uniform consensus of NCCN that this intervention is appropriate.

lymphoma with ≥2 lines of prior chemotherapy and that 5 patients with TFL who had only 1 line of prior post-transformation chemotherapy (all patients with tiNHL [except TFL] had ≥2 lines of prior post-transformation chemotherapy) responded to Breyanzi.

- Patients with ≥2 lines of prior chemotherapy who did not respond to or experienced relapse after the chemotherapy
- Patients with TFL with a total of ≥2 lines of prior chemotherapy including ≥1 line of post-transformation chemotherapy and did not respond to or experienced relapse after the post-transformation chemotherapy

PMDA's view:
It is largely acceptable to determine the "Indication or Performance" based on the results of Studies 017001 and BCM-001. However, the tissue types and prior chemotherapy should be revised in the proposed descriptions for the following reasons:

The "Indications or Performance" section should clearly mention that Breyanzi targets the tissue types of DLBCL, PMBCL, HGBCL, tiNHL, and FL3B, for which the efficacy and safety of Breyanzi was demonstrated in Studies 017001 and BCM-001. Furthermore, FL3B, a type of follicular lymphoma that is not included in large B-cell lymphoma according to the WHO Classification (fourth revision), should thus be described separately from large B-cell lymphoma. Breyanzi is not recommended for the treatment of follicular lymphoma other than FL3B, because the Japanese and foreign clinical practice guidelines clearly differentiate follicular lymphoma other than FL3B from large B-cell lymphoma based on treatment algorithm, and patients with follicular lymphoma other than FL3B were excluded from both Study 017001 and Study BCM-001. Given these, before administering Breyanzi to patients with follicular lymphoma, the tissue type of the lymphoma needs to be confirmed as being FL3B. Accordingly, the "Precautions Concerning Indications or Performance" section should clearly advise that, before administering Breyanzi, patients with follicular lymphoma must be confirmed to have FL3B by a well-experienced pathologist or by a test at an experienced testing facility.

The "Indications or Performance" section should clearly mention that Breyanzi is recommended for patients with tiNHL other than TFL only if they have ≥2 lines of prior post-transformation chemotherapy, based on the prior chemotherapy of this patient population in Study 017001.

In addition, the "Precautions Concerning Indications or Performance" section should note that "eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on knowledge from the "Clinical Studies" section, i.e., the tissue types and prior treatment, etc. of patients enrolled in the clinical studies."

6.R.4.2 HSCT after administration of Breyanzi

The applicant's explanation:
In Study 017001, 12 patients underwent HSCT (allogeneic HSCT in all patients) after administration of Breyanzi, whereas in Study BCM-001, there were no patients who underwent HSCT after administration of Breyanzi.

In Study 017001, the study protocol did not specify the efficacy evaluation after progressive disease (PD)/relapse or after the next anticancer therapy and, as a result, there are no data available on 10 of 12 patients who underwent allogeneic HSCT after Breyanzi infusion. The remaining 2 patients achieved PR following Breyanzi infusion, and their investigator-assessed best response after allogeneic HSCT was PR. As of the data cut-off on August 12, 2019, 2 patients died of disease progression (Day 95 and 505 after allogeneic HSCT) while 10 patients survived. The range of the survival period was 258 to 1,102 days after Breyanzi infusion and 58 to 983 days after allogeneic HSCT. Of the adverse events observed after anticancer therapy including allogeneic HSCT given after Breyanzi infusion, none were reported to have been assessed as causally related to Breyanzi by the investigator.

PMDA's view:
Information about patients who underwent allogeneic HSCT after Breyanzi infusion is very limited. Relevant information should be continuously collected in the post-marketing setting.

6.R.4.3 Patients with a prior treatment with allogeneic HSCT

The applicant's explanation about patients with a prior treatment with allogeneic HSCT:
In the DLBCL safety analysis population of Study 017001, the incidence of all adverse events was similar between patients who had a prior allogeneic HSCT (n = 9) and those who did not a prior allogeneic HSCT (n = 260), whereas the incidence of Grade ≥3 adverse events was higher in patients who had a prior allogeneic HSCT (100%) than in those who did not (78.5%). The grade ≥3 adverse events with a ≥20% higher incidence in patients who had a prior allogeneic HSCT than in those who did not was neutropenia (88.9% vs. 58.8%). The incidence of grade ≥3 adverse events for which a causal relationship to Breyanzi could not be ruled out was higher in patients who did not have a prior allogeneic HSCT (35.4%) than those who did (11.1%). No significant difference was observed in the incidences of CRS and nerve disorder, adverse events requiring particular attention.

PMDA's view:
In Study 017001, the incidence of Grade ≥3 adverse events tended to be higher in patients with a prior allogeneic HSCT, but no significant difference was observed in the safety profile. Nevertheless, Breyanzi has been administered to only a limited number of patients with a prior allogeneic HSCT, safety information in this patient population receiving Breyanzi should be continuously collected in the post-marketing setting.

6.R.4.4 Necessity of confirming CD19 antigen before administration of Breyanzi

PMDA asked the applicant to explain the necessity of confirming CD19 antigen expression before Breyanzi infusion.

The applicant's response:
It is unnecessary to confirm CD19 antigen expression before Breyanzi administration for the following reasons:

- Based on the following results of Studies 017001 and BCM-001, a low or undetectable level of CD19 antigen assessed by an immunohistochemistry (IHC) staining test does not necessarily

means no expression of CD19 antigen, and there is a possibility that CD19 antigen is expressed on the cell surface at a level undetectable by IHC staining test. Furthermore, at present, the accurate threshold of the antigen on tumor cells necessary for activating CAR T cells is unknown (*Nat Commun*. 2019;10:3137). Given these, Breyanzi is expected to show efficacy even if CD19 expression level is below the sensitivity of the existing assays.

  - In Studies 017001 and BCM-001, CD19 antigen expression was evaluated by the IHC assay for an exploratory purpose in 43 patients (5 in Study 017001, 38 in Study BCM-001) using baseline tumor samples. Results found that CD19 antigen was low or undetectable in only 1 patient in Cohort 1 of Study BCM-001, but the patient responded (PR) to the treatment with Breyanzi.

- A majority of large B-cell lymphoma (DLBCL, PMBCL, HGBCL, tiNHL, etc.) and FL3B are positive for CD19 antigen (*Am J Hematol*. 2016;91:E436-41, *Am J Pathol*. 1995;146:735-41, etc.).

PMDA's view:

The above applicant's explanation is understandable. It is unnecessary at present to check for the presence of CD19 antigen before Breyanzi infusion. However, ways to predict the efficacy of Breyanzi prior to the treatment needs to be further discussed so as to make that possible.

6.R.4.5 Administration of Breyanzi to patients with secondary CNS lymphoma

The applicant's explanation:

In Study 017001, both the overall response rate and the rate of CR were 50.0% (95% CI, 11.8-88.2) in 6 patients with secondary CNS lymphoma, suggesting promising efficacy of Breyanzi in this patient population. The incidence of adverse events in the DLBCL safety analysis population was similar between patients who presented with a CNS lesion secondary to lymphoma (n = 7) at the time of Breyanzi infusion and those who did not (n = 262). The incidence of Grade ≥3 adverse events was higher in patients who had a secondary CNS lesion (100% [7 of 7] of patients) than in those who did not (78.6% [206 of 262] of patients), but there was no significant difference in the incidences of CRS, nerve disorder, etc. In Study BCM-001, patients with secondary CNS lymphoma were not enrolled. These findings suggest that Breyanzi administration to patients with secondary CNS lymphoma is recommendable.

PMDA's view:

The above explanation of the applicant is understandable. However, Breyanzi has been administered to only a limited number of patients with secondary CNS lymphoma. Safety information in this patient population receiving Breyanzi should be continuously collected in the post-marketing setting.

6.R.4.6 Breyanzi administration to patients with a prior treatment with anti-CD19 CAR T cells other than Breyanzi

The applicant's explanation:

In the clinical studies of Breyanzi, Breyanzi was not administered to patients with a prior treatment with anti-CD19 CAR T cells other than Breyanzi. The efficacy and safety of Breyanzi in these patients are therefore unclear. In study 017001, 16 patients who experienced PD despite achieving CR after the initial Breyanzi infusion were retreated with Breyanzi (retreatment cycle) at the discretion of the investigator. The overall response rate and the rate of CR after retreatment were 18.8% (3 of 16 of

patients) and 12.5% (2 of 16 of patients), respectively, and the safety profile was similar to that observed after the first dose. Because of the low response rate, the retreatment cycle of Breyanzi was discontinued in Study 017001.

Thus, the possibility cannot be excluded that Breyanzi can benefit patients who were previously treated with anti-CD19 CAR T cells other than Breyanzi and have no other treatment options available, although Breyanzi has never been used in this patient population. Healthcare professionals will be informed via written materials, etc. that there is no use experience of Breyanzi in patients with a prior treatment with anti-CD19 CAR T cells other than Breyanzi.

PMDA's view:
There is no use experience of Breyanzi in this patient population, and the retreatment cycle of Breyanzi was discontinued in Study 017001 because of the low response rate. For these reasons, Breyanzi is not recommendable for patients with a prior treatment with anti-CD19 CAR T cells other than Breyanzi. Given its extreme importance in the decision to choose Breyanzi treatment, this advice should be clearly presented not only in written materials but also in the "Indications or Performance" section of the product.

6.R.5 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" of Breyanzi was as follows:

Leukapheresis at the medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected.
2. Transportation of leukapheresis product
   The leukapheresis product is packed and transported under refrigerated conditions to the manufacturing site of Breyanzi.

Receipt of Breyanzi at medical institution and administration

3. Receipt and keeping of Breyanzi
   Frozen Breyanzi is accepted, and cryopreserved until immediately before use.
4. Treatment before infusion
   Lymphodepleting chemotherapy.
   1) Fludarabine phosphate 30 mg/m^2 and cyclophosphamide (anhydrate) 300 mg/m^2 are infused intravenously once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
   2) Breyanzi is infused 2 to 7 days after the completion of lymphodepleting chemotherapy.
5. Infusion of Breyanzi
   Breyanzi is thawed immediately before infusion. The usual adult dosage is 100×10^6 (irrespective of body weight) CAR-positive viable T cells (CD8-positive and CD4-positive cell components) intravenously infused as a single dose. Refer to the shipping certificate for the actual cell count and dose.

The proposed “Precautions Concerning Dosage and Administration or Method of Use” section included the following advice:
For a series of steps from the collection of cells from the patient to the administration of Breyanzi, refer to the manufacturer’s manual.

If any of the following conditions is observed in the patient, postpone the steps including lymphodepleting chemotherapy and Breyanzi infusion:

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

Administration of Breyanzi

1. Check the patient identification with information on the container of Breyanzi.
2. Check the scheduled infusion timing in advance, and adjust the time to start thawing Breyanzi so that infusion can be started as soon as the patient is ready.
3. Before thawing Breyanzi, check the patient identification with information on the outer box and all vials. Thaw both the CD8-positive cell and CD4-positive cell components in vials at the same time.
4. In order to minimize the risk of injection reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker 30 to 60 minutes before the infusion of Breyanzi. Prophylactic administration of systemic corticosteroid is prohibited because it may inhibit the activity of Breyanzi.
5. Do not use the product in case of any damage or leakage found.
6. Thaw Breyanzi completely at room temperature before infusion. Complete infusion within 2 hours after the vials are taken out of the frozen storage.
7. Handle separately the vial containing CD8-positive cell component and that containing CD4-positive cell component.
8. Have ready syringes for each vial with a patient identification label attached. Withdraw the content of each vial into each designated syringe, and confirm that the volume withdrawn is equal to that indicated in the shipping certificate. For a dose of <2.5 mL, do not use a 5-mL syringe.
9. Do not use a leukocyte-removal filter for Breyanzi infusion.
10. Have ready ≥2 doses of tocilizumab (genetical recombination) and first aid equipment before infusion and during the recovery period.
11. Before infusing Breyanzi, check the patient identification with the syringe label.
12. Infuse the CD8-positive cell components first.
13. Infuse Breyanzi intravenously at approximately 0.5 mL/min.
14. Breyanzi contains human blood cells genetically engineered using self-inactivating lentiviral vector lacking replication competence. Discard as an infectious substance according to the rule at the medical institution.
15. After infusion, monitor the patient 2 to 3 times for ≥1 week for possible signs or symptoms associated with cytokine release syndrome or neurotoxicity at an appropriate medical facility.
16. Instruct the patient to consult with an appropriate medical facility if any symptom is observed

within 4 weeks after infusion.

PMDA's view:

Based on reviews in Sections "6.R.2 Efficacy" and "6.R.3 Safety" as well as the review presented below, the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections of Breyanzi should be modified as follows:

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

Leukapheresis at the medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis product
   The leukapheresis product collected is packed in a refrigerated container set at 1°C to 10°C and transported ~~under refrigerated conditions~~ to the manufacturing site of Breyanzi.

Receipt of Breyanzi at the medical institution and administration

3. Receipt and storage ~~keeping~~ of Breyanzi
   Frozen Breyanzi is accepted and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before infusion
   The patient undergoes a blood test, etc. for condition checking and receives the following ~~L~~lymphodepleting chemotherapy as necessary from 2 to 7 days prior to Breyanzi infusion:
   ~~1)~~ Fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days, and cyclophosphamide (anhydrate) 300 mg/m^2 is infused intravenously once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
   ~~2) Breyanzi is infused 2 to 7 days after lymphodepleting chemotherapy is completed.~~
5. Infusion of Breyanzi
   Breyanzi is thawed immediately before infusion. The usual adult dosage is a total of 100 × 10^6 (range, 44 × 10^6-100 × 10^6 cells) ~~(irrespective of body weight)~~ of CAR-positive viable T cells in total consisting of ~~(~~CD8-positive cells (20 × 10^6-50 × 10^6 cells) and CD4-positive cells ~~components)~~ (20 × 10^6-50 × 10^6 cells), irrespective of body weight. CD8-positive cells are first infused, followed by CD4-positive cells so that the CD8-/CD4-positive cell ratio is 1:1 (range, 0.8-1.2). ~~Refer to the shipping certificate for the actual cell count and dose.~~ Re-administration of Breyanzi is not allowed.

Precautions Concerning Dosage and Administration or Method of Use

For a series of steps from the collection of cells from the patient through the administration of Breyanzi, refer to the manufacturer's manual.

If any of the following conditions is observed in the patient, postpone ~~the steps including~~ lymphodepleting chemotherapy ~~to~~or Breyanzi infusion until recovery:

- Persisting serious adverse events (lung disorder, cardiac disorder, hypotension, etc.) caused by the preceding chemotherapy

- Poorly controlled active infection and inflammatory disease
- Active graft versus host disease (GVHD)

Pretreatment

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

Administration of Breyanzi

1. Check the patient identification with information on the container of Breyanzi.
2. Check the scheduled infusion timing in advance, and adjust the time to start thawing Breyanzi so that infusion can be started as soon as the patient is ready.
3. Before thawing Breyanzi, check the patient identification with information on the outer box and all vials. Thaw both the CD8-positive cell and CD4-positive cell components in vials (4 vials each at the maximum) at the same time.
4. In order to minimize the risk of infusion reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker 30 to 60 minutes before the infusion of Breyanzi. Prophylactic administration of systemic corticosteroid is prohibited because it may inhibit the activity of Breyanzi.
5. Do not use the product in case of any damage or leakage found.
6. Thaw Breyanzi completely at room temperature before infusion. Complete infusion within 2 hours after the vials are taken out of the frozen storage.
7. Handle separately the vial containing CD8-positive cell component and that containing CD4-positive cell component.
8. Check the volume of component indicated on the shipping certificate of each vial, and ~~H~~have ready syringes of a size appropriate for each vial with a patient identification label attached. Withdraw the content of each vial into each designated syringe, and confirm that the volume withdrawn is equal to that indicated in the shipping certificate. ~~For a dose of <2.5 mL, do not use a 5-mL syringe.~~
9. Do not use a leukocyte-removal filter for Breyanzi infusion.
10. Have ready ~~≥2 doses of~~ tocilizumab (genetical recombination) and ~~first aid equipment ready~~ prepare for emergencies before infusion and during the recovery period.
11. Before infusing Breyanzi, check the patient identification with the syringe label.
12. Infuse the CD8-positive cell component first.
13. Infuse Breyanzi intravenously at approximately 0.5 mL/min.
14. Breyanzi contains human blood cells genetically engineered using self-inactivating lentiviral vector lacking replication competence. Discard the residual product as an infectious substance according to the rule at the medical institution.
15. ~~After infusion, monitor the patient 2 to 3 times for ≥1 week for signs or symptoms associated with cytokine release syndrome or neurotoxicity at an appropriate medical facility.~~
16. ~~Instruct the patient to consult with an appropriate medical facility if any symptom is observed within 4 weeks after infusion.~~

6.R.5.1 Dosage regimen of Breyanzi and LD chemotherapy

The applicant's explanation about the rationale for "Dosage and Administration or Method of Use" for Breyanzi and LD chemotherapy:

Dosage regimen of Breyanzi and LD chemotherapy

The dosage regimen of Breyanzi and LD chemotherapy were defined based on the following observations:

- Patients receiving anti-CD19 CAR T cells after LD chemotherapy with fludarabine + cyclophosphamide showed more favorable results in terms of the growth and persistence of anti-CD19 CAR T cells and its anti-tumor effect than in those receiving anti-CD19 CAR T cells after LD chemotherapy with cyclophosphamide alone (*Sci Transl Med*. 2016;8:355ra116), suggesting the benefit of the LD chemotherapy with fludarabine + cyclophosphamide before the treatment with anti-CD19 CAR T cells. Further, antitumor effect was observed following the treatment with fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 for 3 days in patients receiving anti-CD19 CAR T cells, with only a transient nerve disorder (*Molecular Therapy*. 2014;22:S295).
- In Study 017001, the incidences of CRS and nerve disorder were lower in patients receiving a single intravenous dose of 50 or 100 × 10^6 cells of Breyanzi (DL1S or DL2S) than in patients receiving a single intravenous dose of 150 × 10^6 cells of Breyanzi (DL3S).[30)] A single intravenous dose of 100 × 10^6 cells of Breyanzi (DL2S) is selected as the recommended dosage regimen for its more favorable efficacy, etc., than a single intravenous dose of 50 × 10^6 cells of Breyanzi (DL1S), and was administered to a majority of patients (65.8%, 177 of 269 patients). In patients receiving 50 × 10^6 cells of Breyanzi twice 14 days apart (DL1D), the increase in anti-CD19 CAR T cells was not clear after the second dose, whereupon the study on DL1D, the double-dose regimen, was discontinued.
- Studies 017001 and BCM-001 confirmed the efficacy and safety of administering 100 × 10^6 cells of Breyanzi following the LD chemotherapy with fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 for 3 days in patients (including Japanese) with relapsed or refractory large B-cell lymphoma.
- In Study 017001, the lowest dose of Breyanzi administered intravenously in a single dose (DL1S, DL2S, or DL3S) was 20 × 10^6 each of CD8-positive and CD4-positive T cells, with the lowest total dose being 44 × 10^6 cells.

CD8-positive T cells and CD4-positive T cells of the product are manufactured separately, and the ratio of the number of each cell to be administered is controlled. Results of a nonclinical study showed that anti-CD19 CAR T cells with a prespecified ratio of CD8-positive to CD4-positive T cells have an augmented anti-tumor activity as compared to anti-CD19 CAR T cells derived from non-selectively harvested T cells (*Leukemia.* 2016;30:492-500). Also, a relationship between the administration of high-dose CD8-positive T cells and nerve disorder, etc. was suggested from clinical studies of an anti-CD19 CAR T cell product with an unspecified ratio of CD8-positive to CD4-positive T cells,

30) The incidence of all Grade CRS was 40.0% with DL1S, 37.3% with DL2S, and 63.4% with DL3S, and the incidence of all Grade nerve disorder identified by the investigator was 22.2% with DL1S, 29.9% with DL2S, and 39.0% with DL3S, showing that the incidences were higher with DL3S than with DL1S or DL2S. Also, the incidence of Grade ≥3 infection was higher with DL3S than with DL2S or DL1S (DL1S:8.9%, DL2S:11.3%, DL3S:22.0%).

which was developed by Juno, Inc. ahead of Breyanzi. Given these, and based on the median ratio (range) of CD8-positive to CD4-positive T cells administered being 1 (0.7-1.3) in approximately 94% of patients in Study 017001, the ratio (range) of CD8-positive to CD4-positive T cells in Breyanzi was determined to be 1 (0.8-1.2).

Also, by taking account of the report suggesting that whereas CD8-positive T cells have mainly an anti-tumor effect, CD4-positive T cells enhance migratory and cytotoxic activities, etc. of CD8-positive T cells (*Exp Med*. 1999;189:753-6, *Cancer Res*. 2010;70:8368-77, etc.), CD8-positive T cells were administered first in Studies 017001 and BCM-001. Therefore, it is appropriate to administer CD8-positive T cells ahead of CD4-positive T cells.

Use of LD chemotherapy

In Studies 017001 and BCM-001, LD chemotherapy was allowed in patients who had a PET-positive lesion and sufficient organ functions, and met the criteria for active infection and pregnancy. Also, the effect of prior treatment was needed to be washed out. In Study BCM-001, because of a reported case of patient experiencing respiratory failure that resulted in death, an additional criterion was added so that LD chemotherapy and Breyanzi infusion were not allowed for patients presenting with a worsening condition equivalent to Eastern Cooperative Oncology Group performance status (ECOG PS) score to 2, rapidly deteriorated clinical conditions, or abrupt disease progression. In Studies 017001 and BCM-001, all patients receiving Breyanzi had received prior LD chemotherapy, and Breyanzi was never administered to patients who had not received LD chemotherapy.

Advance LD chemotherapy is an essentially required before the administration of Breyanzi. Nevertheless, assuming different situations of patients before LD chemotherapy in the clinical setting, physicians will be advised to determine the use of LD chemotherapy depending on the patient's condition via the "Dosage and Administration or Method of Use" section. The "Clinical Studies" section of the package insert will elaborate the LD chemotherapy used in the clinical studies.

Administration of Breyanzi in the outpatient setting

Table 53 shows the incidences of adverse events in 25 patients in the DLBCL cohort of Study 017001 who received Breyanzi in the outpatient setting.[31)] Results were similar to those observed in 244 patients receiving Breyanzi under hospitalization (In Study BCM-001, there were no patients who received Breyanzi in the outpatient setting). These results suggest that the outpatient administration of Breyanzi is feasible on the premise that healthcare professionals are provided with appropriate information and advice via the package insert, etc. to control adverse events associated with Breyanzi infusion.

[31)] In Study 017001, patients were regarded as treated at an outpatient visit if the day of the first dose of Breyanzi did not overlap the hospitalization period.

Table 53. Summary of safety in Breyanzi administration in the outpatient setting, and hospitalization conditions (Study 017001 [DLBCL cohort])

	Number of patients (%)	
	Outpatients in Study 017001 (DLBCL cohort) n = 25	Inpatients in Study 017001 (DLBCL cohort) n = 244
All adverse events	25 (100)	242 (99.2)
Grade ≥ 3 adverse events	17 (68.0)	196 (80.3)
Serious adverse events	18 (72.0)	104 (42.6)
Adverse events resulting in death	0	7 (2.9)
CRS	12 (48.0)	101 (41.4)
Grade ≥3 CRS	1 (4.0)	5 (2.0)
iiNT	11 (44.0)	69 (28.3)
Grade ≥3 iiNT	2 (8.0)	25 (10.2)
Patients hospitalized (%)	18 (72.0)	244 (100)
Time to initial hospitalization (days) Median (range)	5.0 (3-22)	-
Period[b)] of initial hospitalization[a)] (days) Median (range)	6.0 (2-23)	11.0 (3-88)
Patients admitted to ICU during the initial hospitalization[a)] (%)	1 (4.0)	18 (7.4)

a) "Hospitalization for Breyanzi administration" in patients receiving the administration under hospitalization
b) "Time from Breyanzi administration to discharge" in patients receiving the administration under hospitalization

The safety monitoring after Breyanzi infusion revealed that most of CRS and nerve disorder observed in Studies 017001 and BCM-001 occurred within 1 week after Breyanzi infusion, and that, in Study 017001, CRS preceded iiNT in 72.5% (58 of 80) of patients with iiNT, indicating the importance of monitoring for CRS and nerve disorder during 1 week after Breyanzi infusion. In Studies 017001 and BCM-001, precise safety monitoring including ≥2 blood testing was performed within 1 week after Breyanzi infusion. In the post-marketing setting as well, patients should be monitored for 2 to 3 times within 1 week after administration at the medical institution where they are treated with Breyanzi, as practiced in the clinical studies.

Re-administration of Breyanzi

In Study 017001, in addition to patients on the DL1D regimen with intravenous infusion of Breyanzi (50×10^6 cells) twice 14 days apart, other patients were allowed to undergo the re-administration of Breyanzi only if they once achieved CR after Breyanzi infusion but suffered PD later, or if their BOR after the first assessment of the treatment effect following Breyanzi infusion was stable disease (SD) or PR.

A total of 16 patients who had once achieved CR after Breyanzi infusion and suffered PD thereafter underwent re-administration. Of these, 3 patients responded (CR in 1, PR in 2) while the remaining 13 patients failed to respond (SD in 3, PD in 10). A total of 7 patients whose BOR was SD or PR at the first efficacy assessment after Breyanzi infusion and underwent re-administration, 2 patients responded (CR in 2) while the remaining 5 patients failed to respond (PD in 5). These results suggested that the re-administration of Breyanzi is unlikely to benefit patients. Accordingly, the protocol of Study 017001 was revised with deleted rule for re-administration of Breyanzi to patients who failed to achieve CR after Breyanzi infusion.

Thus, it is difficult to evaluate the risks and benefits of re-administration of Breyanzi based on the data

of Study 017001. The lack of established efficacy and safety of Breyanzi re-administration will be communicated via written materials.

PMDA's view:
The applicant's explanation about the dosage regimens of Breyanzi and LD chemotherapy is understandable. However, taking into account that Breyanzi is composed of CD8-positive T cells in vial and CD4-positive T cells in vial, the ranges of the numbers of CD8-positive T cells and CD4-positive T cells to be administered, the range of the sum of both types of cells to be administered, and the ratio of these cell numbers to be administered are important information, and should be clearly mentioned in the "Dosage and Administration or Method of Use" section. In Studies 017001 and BCM-001, Breyanzi infusion was started with CD8-positive T cells. Given its importance, the order of administration should be clearly advised in the "Dosage and Administration or Method of Use" section.

LD chemotherapy, which is aimed to facilitate the engraftment of Breyanzi in the body, should be performed according to pre-assessed patient's condition, and that should be clearly mentioned in the "Dosage and Administration or Method of Use" section, taking into account that some patients eligible for Breyanzi may need to undergo anticancer therapy (bridging chemotherapy) for disease control during the Breyanzi manufacturing period after leukapheresis.

Breyanzi infusion in the outpatient setting may pose a safety concern. Adverse events such as CRS and nerve disorder occurred frequently the early phase after Breyanzi infusion with some serious cases. Therefore, patients should undergo Breyanzi infusion and precise monitoring under hospitalization [see Sections 6.R.3.2.1 and 6.R.3.2.3]. The descriptions of the "Precautions Concerning Dosage and Administration or Method of Use" section should be modified to advise appropriate safety monitoring after Breyanzi infusion. Healthcare professionals should also be provided with appropriate information and advice via the "Important Precautions" section of the package insert and written materials.

The re-administration of Breyanzi is not recommended at present. The efficacy and safety of re-administration have not been established because of limited experience. This is important information, and the "Dosage and Administration or Method of Use" section should highlight that Breyanzi should not be re-administered even if disease progression occurs.

The other points of applicant's explanation are understandable.

7. Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation about the post-marketing surveillance plan for Breyanzi:
In order to investigate the safety of Breyanzi in clinical use, etc., the applicant plans post-marketing surveillance covering all patients with relapsed or refractory large B-cell lymphoma.

The safety specification of the surveillance include the following:
"CRS," "neurotoxicity," "infection," "hypogammaglobulinemia," "macrophage activation syndrome (hemophagocytic lymphohistiocytosis)," "tumour lysis syndrome," "hematocytopenia (including bone

marrow failure),” “autoimmune disorder,” “graft versus host disease aggravation,” “secondary carcinogenesis (including carcinogenesis due to insertional mutagenesis caused by lentiviral vector),” and “brain edema,” which are adverse events anticipated to occur in the post-marketing setting based on their occurrence in in Studies 017001 and BCM-001; and “Effect on pregnancy or breast-feeding,” “long-term safety,” and “administration to children” as missing information on Breyanzi.

The surveillance plans to cover 300 patients based on the number of patients expected to receive Breyanzi in the post-marketing setting (over 2 years after the market launch of Breyanzi) in consideration of the importance of long-term follow-up and the incidences of the events i.e., those included in the safety specifications, in Studies 017001 and BCM-001.

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

PMDA’s view:
Because of extremely limited safety data of Breyanzi from Japanese patients, the applicant should collect post-marketing data from all treated patients and provide healthcare professionals with available safety information promptly.

The safety specification of surveillance covering all treated patients should include “hypersensitivity,” taking account of the review in Section “6.R.3. Safety.”

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

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

8. Adverse Events Observed in Clinical Studies

Data on death reported in the clinical studies submitted for safety evaluation are presented in Section “6.1 Evaluation data.” Main adverse events other than death are shown below.

8.1 Foreign phase I study (Study 017001)

In the DLBCL cohort, adverse events were observed in 267 of 269 patients (99.3%). Adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 201 of 269 patients (74.7%). Tables 54 and 55 show adverse events with an all Grade incidence of ≥10%.

Table 54. Adverse events with an incidence of ≥10%
(Study 017001, DLBCL cohort, DL2S, DL1S, and DL1D groups)

System organ class	Number of patients (%)					
	DL2S (n = 177)		DL1S (n = 45)		DL1D (n = 6)	
PT (MedDRA ver. 21.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	177 (100)	140 (79.1)	44 (97.8)	36 (80.0)	6 (100)	5 (83.3)
Blood and lymphatic system disorders						
Neutropenia	110 (62.1)	106 (59.9)	31 (68.9)	28 (62.2)	5 (83.3)	5 (83.3)
Anaemia	80 (45.2)	64 (36.2)	24 (53.3)	20 (44.4)	3 (50.0)	1 (16.7)
Thrombocytopenia	55 (31.1)	49 (27.7)	14 (31.1)	13 (28.9)	4 (66.7)	3 (50.0)
Leukopenia	30 (16.9)	26 (14.7)	10 (22.2)	10 (22.2)	1 (16.7)	1 (16.7)
Febrile neutropenia	13 (7.3)	13 (7.3)	5 (11.1)	4 (8.9)	0	0
General disorders and administration site conditions						
Fatigue	81 (45.8)	4 (2.3)	19 (42.2)	0	2 (33.3)	0
Pyrexia	33 (18.6)	0	6 (13.3)	0	1 (16.7)	0
Oedema peripheral	26 (14.7)	1 (0.6)	9 (20.0)	0	0	0
Chills	16 (9.0)	0	6 (13.3)	0	2 (33.3)	0
Pain	20 (11.3)	0	5 (11.1)	1 (2.2)	0	0
Asthenia	15 (8.5)	4 (2.3)	1 (2.2)	0	0	0
Gastrointestinal disorders						
Nausea	57 (32.2)	4 (2.3)	15 (33.3)	0	3 (50.0)	0
Diarrhoea	48 (27.1)	1 (0.6)	9 (20.0)	0	3 (50.0)	0
Constipation	39 (22.0)	0	12 (26.7)	0	1 (16.7)	0
Vomiting	30 (16.9)	1 (0.6)	12 (26.7)	0	2 (33.3)	0
Abdominal pain	31 (17.5)	4 (2.3)	6 (13.3)	1 (2.2)	0	0
Dyspepsia	10 (5.6)	0	2 (4.4)	0	1 (16.7)	0
Abdominal distension	6 (3.4)	0	1 (2.2)	0	1 (16.7)	0
Small intestinal obstruction	1 (0.6)	0	0	0	1 (16.7)	0
Nervous system disorders						
Headache	56 (31.6)	3 (1.7)	11 (24.4)	0	1 (16.7)	0
Dizziness	39 (22.0)	1 (0.6)	11 (24.4)	0	2 (33.3)	0
Tremor	29 (16.4)	0	3 (6.7)	0	0	0
Encephalopathy	8 (4.5)	5 (2.8)	6 (13.3)	4 (8.9)	1 (16.7)	1 (16.7)
Metabolism and nutrition disorders						
Decreased appetite	50 (28.2)	6 (3.4)	15 (33.3)	0	1 (16.7)	0
Hypokalaemia	40 (22.6)	5 (2.8)	6 (13.3)	1 (2.2)	0	0
Hypomagnesaemia	32 (18.1)	0	11 (24.4)	0	0	0
Hypophosphataemia	15 (8.5)	10 (5.6)	3 (6.7)	1 (2.2)	0	0
Dehydration	14 (7.9)	2 (1.1)	3 (6.7)	1 (2.2)	1 (16.7)	0
Hyperlipidaemia	2 (1.1)	0	0	0	1 (16.7)	0
Respiratory, thoracic and mediastinal disorders						
Cough	41 (23.2)	0	9 (20.0)	0	0	0
Dyspnoea	26 (14.7)	2 (1.1)	5 (11.1)	0	0	0
Oropharyngeal pain	12 (6.8)	0	3 (6.7)	0	1 (16.7)	0
Hypoxia	8 (4.5)	1 (0.6)	5 (11.1)	2 (4.4)	0	0
Epistaxis	12 (6.8)	1 (0.6)	0	0	1 (16.7)	0
Atelectasis	2 (1.1)	0	5 (11.1)	0	0	0
Tachypnoea	3 (1.7)	0	0	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders						
Back pain	19 (10.7)	1 (0.6)	9 (20.0)	1 (2.2)	1 (16.7)	0
Arthralgia	17 (9.6)	1 (0.6)	3 (6.7)	1 (2.2)	0	0
Pain in extremity	14 (7.9)	1 (0.6)	4 (8.9)	1 (2.2)	1 (16.7)	0
Flank pain	6 (3.4)	0	2 (4.4)	1 (2.2)	1 (16.7)	0
Immune system disorders						
Cytokine release syndrome	66 (37.3)	5 (2.8)	18 (40.0)	1 (2.2)	3 (50.0)	0
Hypogammaglobulinaemia	28 (15.8)	0	3 (6.7)	0	1 (16.7)	0
Infections and infestations						
Pneumonia	13 (7.3)	6 (3.4)	1 (2.2)	1 (2.2)	1 (16.7)	0
Clostridium difficile infection	6 (3.4)	0	1 (2.2)	1 (2.2)	1 (16.7)	0
Nasopharyngitis	0	0	0	0	1 (16.7)	0
Vascular disorders						
Hypotension	41 (23.2)	8 (4.5)	10 (22.2)	0	0	0
Hypertension	20 (11.3)	5 (2.8)	10 (22.2)	4 (8.9)	1 (16.7)	0

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) DL2S (n = 177)		DL1S (n = 45)		DL1D (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Deep vein thrombosis	5 (2.8)	2 (1.1)	4 (8.9)	0	1 (16.7)	0
Psychiatric disorders						
Confusional state	25 (14.1)	1 (0.6)	5 (11.1)	0	0	0
Insomnia	26 (14.7)	1 (0.6)	5 (11.1)	0	0	0
Anxiety	17 (9.6)	0	9 (20.0)	0	0	0
Cardiac disorders						
Sinus tachycardia	23 (13.0)	0	11 (24.4)	0	2 (33.3)	0
Skin and subcutaneous tissue disorders						
Night sweats	13 (7.3)	0	2 (4.4)	0	1 (16.7)	0
Rash	6 (3.4)	0	3 (6.7)	0	2 (33.3)	0
Dry skin	3 (1.7)	0	1 (2.2)	0	1 (16.7)	0
Ecchymosis	1 (0.6)	0	1 (2.2)	0	1 (16.7)	0
Renal and urinary disorders						
Urinary incontinence	5 (2.8)	0	3 (6.7)	0	0	0
Eye disorders						
Conjunctival haemorrhage	0	0	1 (2.2)	0	1 (16.7)	0
Eye pruritus	0	0	0	0	1 (16.7)	0
Reproductive system and breast disorders						
Benign prostatic hyperplasia	4 (2.3)	0	1 (2.2)	0	1 (16.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Malignant pleural effusion	2 (1.1)	2 (1.1)	0	0	1 (16.7)	1 (16.7)

Table 55. Adverse events with an incidence of ≥10%
(Study 017001, DLBCL cohort, DL3S group, all patients)

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) DL3S (n = 41)		All patients (n = 269)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	40 (97.6)	32 (78.0)	267 (99.3)	213 (79.2)
Blood and lymphatic system disorders				
Neutropenia	23 (56.1)	22 (53.7)	169 (62.8)	161 (59.9)
Anaemia	22 (53.7)	16 (39.0)	129 (48.0)	101 (37.5)
Thrombocytopenia	11 (26.8)	7 (17.1)	84 (31.2)	72 (26.8)
Leukopenia	3 (7.3)	2 (4.9)	44 (16.4)	39 (14.5)
Febrile neutropenia	7 (17.1)	7 (17.1)	25 (9.3)	24 (8.9)
General disorders and administration site conditions				
Fatigue	17 (41.5)	0	119 (44.2)	4 (1.5)
Pyrexia	5 (12.2)	0	45 (16.7)	0
Oedema peripheral	7 (17.1)	0	42 (15.6)	1 (0.4)
Chills	7 (17.1)	0	31 (11.5)	0
Pain	0	0	25 (9.3)	1 (0.4)
Asthenia	6 (14.6)	1 (2.4)	22 (8.2)	5 (1.9)
Gastrointestinal disorders				
Nausea	15 (36.6)	0	90 (33.5)	4 (1.5)
Diarrhoea	11 (26.8)	0	71 (26.4)	1 (0.4)
Constipation	10 (24.4)	0	62 (23.0)	0
Vomiting	12 (29.3)	0	56 (20.8)	1 (0.4)
Abdominal pain	7 (17.1)	0	44 (16.4)	5 (1.9)
Dyspepsia	3 (7.3)	0	16 (5.9)	0
Abdominal distension	3 (7.3)	0	11 (4.1)	0
Small intestinal obstruction	0	0	2 (0.7)	0
Nervous system disorders				
Headache	12 (29.3)	0	80 (29.7)	3 (1.1)
Dizziness	8 (19.5)	0	60 (22.3)	1 (0.4)
Tremor	9 (22.0)	0	41 (15.2)	0
Encephalopathy	4 (9.8)	2 (4.9)	19 (7.1)	12 (4.5)
Metabolism and nutrition disorders				
Decreased appetite	10 (24.4)	1 (2.4)	76 (28.3)	7 (2.6)
Hypokalaemia	6 (14.6)	0	52 (19.3)	6 (2.2)
Hypomagnesaemia	7 (17.1)	0	50 (18.6)	0
Hypophosphataemia	9 (22.0)	5 (12.2)	27 (10.0)	16 (5.9)
Dehydration	4 (9.8)	0	22 (8.2)	3 (1.1)

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) DL3S (n = 41) All Grades	 Grade ≥3	 All patients (n = 269) All Grades	 Grade ≥3
Hyperlipidaemia	1 (2.4)	0	4 (1.5)	0
Respiratory, thoracic and mediastinal disorders				
Cough	7 (17.1)	0	57 (21.2)	0
Dyspnoea	5 (12.2)	0	36 (13.4)	2 (0.7)
Oropharyngeal pain	1 (2.4)	0	17 (6.3)	0
Hypoxia	2 (4.9)	0	15 (5.6)	3 (1.1)
Epistaxis	0	0	13 (4.8)	1 (0.4)
Atelectasis	0	0	7 (2.6)	0
Tachypnoea	0	0	4 (1.5)	0
Musculoskeletal and connective tissue disorders				
Back pain	4 (9.8)	1 (2.4)	33 (12.3)	3 (1.1)
Arthralgia	6 (14.6)	0	26 (9.7)	2 (0.7)
Pain in extremity	1 (2.4)	0	20 (7.4)	2 (0.7)
Flank pain	2 (4.9)	0	11 (4.1)	1 (0.4)
Immune system disorders				
Cytokine release syndrome	26 (63.4)	0	113 (42.0)	6 (2.2)
Hypogammaglobulinaemia	5 (12.2)	0	37 (13.8)	0
Infections and infestations				
Pneumonia	1 (2.4)	1 (2.4)	16 (5.9)	8 (3.0)
Clostridium difficile infection	1 (2.4)	0	9 (3.3)	1 (0.4)
Nasopharyngitis	1 (2.4)	0	2 (0.7)	0
Vascular disorders				
Hypotension	9 (22.0)	0	60 (22.3)	8 (3.0)
Hypertension	6 (14.6)	3 (7.3)	37 (13.8)	12 (4.5)
Deep vein thrombosis	1 (2.4)	0	11 (4.1)	2 (0.7)
Psychiatric disorders				
Confusional state	9 (22.0)	1 (2.4)	39 (14.5)	2 (0.7)
Insomnia	5 (12.2)	0	36 (13.4)	1 (0.4)
Anxiety	1 (2.4)	0	27 (10.0)	0
Cardiac disorders				
Sinus tachycardia	6 (14.6)	0	42 (15.6)	0
Skin and subcutaneous tissue disorders				
Night sweats	0	0	16 (5.9)	0
Rash	2 (4.9)	0	13 (4.8)	0
Dry skin	3 (7.3)	0	8 (3.0)	0
Ecchymosis	0	0	3 (1.1)	0
Renal and urinary disorders				
Urinary incontinence	5 (12.2)	0	13 (4.8)	0
Eye disorders				
Conjunctival haemorrhage	0	0	2 (0.7)	0
Eye pruritus	0	0	1 (0.4)	0
Reproductive system and breast disorders				
Benign prostatic hyperplasia	1 (2.4)	0	7 (2.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant pleural effusion	0	0	3 (1.1)	3 (1.1)

In the MCL cohort, adverse events were observed in 17 of 17 patients (100%). Adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 14 of 17 patients (82.4%). Table 56 shows adverse events with an all Grade incidence of ≥20%.

Table 56. Adverse events with an incidence of ≥20%
(Study 017001, MCL cohort, DL2S, DL1S, and both groups combined)

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) DL2S (n = 11)		DL1S (n = 6)		Both groups combined (n = 17)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	11 (100)	10 (90.9)	6 (100)	4 (66.7)	17 (100)	14 (82.4)
Blood and lymphatic system disorders						
Anaemia	6 (54.5)	5 (45.5)	3 (50.0)	2 (33.3)	9 (52.9)	7 (41.2)
Neutropenia	4 (36.4)	4 (36.4)	3 (50.0)	2 (33.3)	7 (41.2)	6 (35.3)
Thrombocytopenia	5 (45.5)	5 (45.5)	1 (16.7)	1 (16.7)	6 (35.3)	6 (35.3)
Febrile neutropenia	3 (27.3)	2 (18.2)	0	0	3 (17.6)	2 (11.8)
Metabolism and nutrition disorders						
Decreased appetite	2 (18.2)	1 (9.1)	2 (33.3)	0	4 (23.5)	1 (5.9)
Hypomagnesaemia	1 (9.1)	0	2 (33.3)	0	3 (17.6)	0
Vascular disorders						
Hypotension	4 (36.4)	0	0	0	4 (23.5)	0
Immune system disorders						
Cytokine release syndrome	7 (63.6)	1 (9.1)	2 (33.3)	0	9 (52.9)	1 (5.9)
Nervous system disorders						
Headache	3 (27.3)	0	1 (16.7)	0	4 (23.5)	0
Insomnia	3 (27.3)		1 (16.7)		4 (23.5)	
Anxiety	3 (27.3)				3 (17.6)	
Musculoskeletal and connective tissue disorders						
Muscular weakness	2 (18.2)	0	2 (33.3)	0	4 (23.5)	0
Back pain	1 (9.1)	0	2 (33.3)	1 (9.1)	3 (17.6)	1 (5.9)
Neck pain	0	0	2 (33.3)	0	2 (11.8)	0
General disorders and administration site conditions						
Fatigue	2 (18.2)	1 (9.1)	3 (50.0)	0	5 (29.4)	1 (5.9)
Psychiatric disorders						
Insomnia	3 (27.3)	0	1 (16.7)	0	4 (23.5)	0
Skin and subcutaneous tissue disorders						
Night sweats	0	0	2 (33.3)	0	2 (11.8)	1 (5.9)
Renal and urinary disorders						
Acute kidney injury	3 (27.3)	0	1 (16.7)	0	4 (23.5)	0

In the DLBCL cohort, serious adverse events were observed in 122 of 269 patients (45.4%). Serious adverse events observed in ≥3 patients were cytokine release syndrome in 44 patients (16.4%), encephalopathy in 14 patients (5.2%), neutropenia in 11 patients (4.1%), febrile neutropenia, thrombocytopenia, and pyrexia in 10 patients (3.7%) each, aphasia in 9 patients (3.3%), pneumonia, confusional state, and hypotension in 8 patients (3.0%) each, mental status changes in 7 patients (2.6%), anaemia in 5 patients (1.9%), syncope, sepsis, and agitation in 4 patients (1.5%) each, tremor, Clostridium difficile infection, septic shock, asthenia, abdominal pain, respiratory failure, dehydration, and acute kidney injury in 3 patients (1.1%) each. A causal relationship to Breyanzi could not be ruled out for cytokine release syndrome in 44 patients, encephalopathy in 12 patients, aphasia in 9 patients, confusional state in 8 patients, mental status change, neutropenia, and thrombocytopenia in 6 patients each, febrile neutropenia in 5 patients, agitation, pneumonia, and hypotension in 4 patients each, tremor and sepsis in 3 patients each, pyrexia and acute kidney injury in 2 patients each, anaemia, asthenia, and dehydration in 1 patient each.

In the MCL cohort, serious adverse events were observed in 10 of 17 patients (58.8%). The serious adverse event observed in ≥2 patients was cytokine release syndrome in 4 patients, and its causal relationship to Breyanzi could not be ruled out in all of them.

8.2 Global phase II study (Study BCM-001)

Adverse events were observed in all patients. Adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 42 of 46 patients (91.3%). Table 57 shows adverse events with an all Grade incidence of ≥10%.

Table 57. Adverse events with an incidence of ≥10% (Study BCM-001)

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) Cohort 1 (n = 36)		Cohort 3 (n = 10)		Both cohorts combined (n = 46)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	36 (100.0)	34 (94.4)	10 (100.0)	9 (90.0)	46 (100.0)	43 (93.5)
Blood and lymphatic system disorders						
Neutropenia	32 (88.9)	30 (83.3)	9 (90.0)	9 (90.0)	41 (89.1)	39 (84.8)
Anaemia	18 (50.0)	11 (30.6)	8 (80.0)	7 (70.0)	26 (56.5)	18 (39.1)
Thrombocytopenia	16 (44.4)	9 (25.0)	9 (90.0)	7 (70.0)	25 (54.3)	16 (34.8)
Leukopenia	8 (22.2)	8 (22.2)	9 (90.0)	8 (80.0)	17 (37.0)	16 (34.8)
Lymphopenia	9 (25.0)	7 (19.4)	0	0	9 (19.6)	7 (15.2)
Febrile neutropenia	8 (22.2)	8 (22.2)	0	0	8 (17.4)	8 (17.4)
Hypofibrinogenaemia	1 (2.8)	1 (2.8)	4 (40.0)	2 (20.0)	5 (10.9)	3 (6.5)
Acquired antithrombin III deficiency	0	0	1 (10.0)	0	1 (2.2)	0
Eosinophilia	0	0	1 (10.0)	0	1 (2.2)	0
General disorders and administration site conditions						
Pyrexia	19 (52.8)	0	1 (10.0)	0	20 (43.5)	0
Fatigue	2 (5.6)	0	4 (40.0)	0	6 (13.0)	0
Oedema peripheral	2 (5.6)	1 (2.8)	1 (10.0)	0	3 (6.5)	1 (2.2)
Catheter site related reaction	0	0	1 (10.0)	0	1 (2.2)	0
Infusion site rash	0	0	1 (10.0)	0	1 (2.2)	0
Multiple organ dysfunction syndrome	0	0	1 (10.0)	1 (10.0)	1 (2.2)	1 (2.2)
Immune system disorders						
Cytokine release syndrome	14 (38.9)	2 (5.6)	5 (50.0)	0	19 (41.3)	2 (4.3)
Hypogammaglobulinaemia	4 (11.1)	0	2 (20.0)	0	6 (13.0)	0
Gastrointestinal disorders						
Constipation	7 (19.4)	0	1 (10.0)	0	8 (17.4)	0
Diarrhoea	5 (13.9)	1 (2.8)	1 (10.0)	0	6 (13.0)	1 (2.2)
Nausea	5 (13.9)	0	1 (10.0)	1 (10.0)	6 (13.0)	1 (2.2)
Abdominal pain	4 (11.1)	1 (2.8)	0	0	4 (8.7)	1 (2.2)
Vomiting	2 (5.6)	0	1 (10.0)	0	3 (6.5)	0
Melaena	0	0	1 (10.0)	0	1 (2.2)	0
Nervous system disorders						
Headache	7 (19.4)	0	0	0	7 (15.2)	0
Tremor	5 (13.9)	1 (2.8)	0	0	5 (10.9)	1 (2.2)
Aphasia	4 (11.1)	3 (8.3)	0	0	4 (8.7)	3 (6.5)
Post herpetic neuralgia	0	0	1 (10.0)	0	1 (2.2)	0
Infections and infestations						
Varicella zoster virus infection	0	0	1 (10.0)	0	1 (2.2)	0
Metabolism and nutrition disorders						
Hypomagnesaemia	6 (16.7)	0	1 (10.0)	0	7 (15.2)	0
Hypokalaemia	5 (13.9)	1 (2.8)	1 (10.0)	0	6 (13.0)	1 (2.2)
Decreased appetite	1 (2.8)	0	1 (10.0)	0	2 (4.3)	0
Musculoskeletal and connective tissue disorders						
Bone pain	4 (11.1)	0	0	0	4 (8.7)	0
Pain in extremity	4 (11.1)	0	0	0	4 (8.7)	0
Skin and subcutaneous tissue disorders						
Dermatitis acneiform	1 (2.8)	0	1 (10.0)	0	2 (4.3)	0
Rash	1 (2.8)	0	1 (10.0)	0	2 (4.3)	0
Respiratory, thoracic and mediastinal disorders						
Cough	4 (11.1)	0	0	0	4 (8.7)	0
Hiccups	2 (5.6)	0	1 (10.0)	0	3 (6.5)	0
Hypoxia	1 (2.8)	1 (2.8)	1 (10.0)	1 (10.0)	2 (4.3)	2 (4.3)
Psychiatric disorders						

System organ class PT (MedDRA ver. 21.0)	Number of patients (%) Cohort 1 (n = 36)		Cohort 3 (n = 10)		Both cohorts combined (n = 46)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Confusional state	6 (16.7)	3 (8.3)	1 (10.0)	0	7 (15.2)	3 (6.5)
Delirium	2 (5.6)	2 (5.6)	1 (10.0)	0	3 (6.5)	2 (4.3)
Injury, poisoning and procedural complications						
Allergic transfusion reaction	0	0	2 (20.0)	0	2 (4.3)	0
Post procedural haemorrhage	0	0	1 (10.0)	0	1 (2.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Peritumoural oedema	0	0	1 (10.0)	1 (10.0)	1 (2.2)	1 (2.2)

Serious adverse events were observed in 20 of 46 patients (43.5%). Serious adverse events observed in ≥2 patients were cytokine release syndrome in 7 patients (15.2%), confusional state in 5 patients (10.9%), febrile neutropenia, aphasia, and tremor in 4 patients (8.7%) each, histiocytosis haematophagic, Candida sepsis, memory impairment, somnolence, delirium, disorientation, and abdominal pain in 2 patients (4.3%) each. A causal relationship to Breyanzi could not be ruled out for cytokine release syndrome in 7 patients, confusional state in 5 patients, aphasia and tremor in 4 patients each, febrile neutropenia in 3 patients, memory impairment, somnolence, delirium, disorientation, histiocytosis haematophagic, and Candida sepsis in 2 patients each.

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

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

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

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

The new regenerative medical product application data (CTD 5.3.5.2.3) 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.

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

On the basis of the data submitted, PMDA has concluded that Breyanzi has efficacy to a certain extent in the treatment of relapsed or refractory large B-cell lymphoma and relapsed or refractory follicular lymphoma, and that Breyanzi has acceptable safety in view of its benefits. Accordingly, it is of significance to make Breyanzi available in the clinical practice because it offers a new treatment option for patients with DLBCL, PMBCL, tiNHL, HGBCL, and FL3B.

PMDA has concluded that Breyanzi may be approved if Breyanzi is not considered to have any

particular problems based on comments from the Expert Discussion.

Review Report (2)

February 1, 2021

Product Submitted for Approval

Brand Name	Breyanzi Suspension for Intravenous Infusion
Non-proprietary Name	Lisocabtagene Maraleucel
Applicant	Celgene Corporation
Date of Application	June 22, 2020

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 review in Section "6.R.2 Efficacy," of the Review Report (1), the overall response rate, the primary efficacy endpoint of Studies 017001 and BCM-001 conducted in patients with relapsed or refractory DLBCL, PMBCL, HGBCL, tiNHL, and FL3B, was greater than the predefined efficacy threshold. PMDA, therefore, concluded that the efficacy of Breyanzi has been demonstrated to a certain extent in patients with relapsed or refractory DLBCL, PMBCL, HGBCL, tiNHL, and FL3B.

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

1.2 Safety

As a result of the review in Section "6.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention in Breyanzi treatment are CRS, hemophagocytic lymphohistiocytosis, nerve disorder, infection, bone marrow depression, hypersensitivity, hypogammaglobulinemia, and TLS. Caution should be exercised against these adverse events in the use of Breyanzi.

In addition, PMDA concluded that Breyanzi is tolerable, given appropriate measures i.e., monitoring and management of adverse events taken by a physician with sufficient knowledge and experience in the treatment of DLBCL, PMBCL, HGBCL, tiNHL, and FL3B at a medical institution well-equipped for dealing with these adverse events.

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

1.3 Clinical positioning and indication or performance

As a result of the review in Section "6.R.4 Clinical positioning and indication or performance," PMDA concluded that the tissue types and prior treatments of patients enrolled in Studies 017001 and BCM-001 should be detailed in the "Clinical Studies" section of the package insert, and that the "Indication or Performance" and "Precautions Concerning Indications or Performance" sections should be described as per the relevant sections of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. Meanwhile, the following comments were raised:

- The Japanese clinical practice guideline (Practical Guidelines for Hematological Malignancies, 2018 revised edition [Japanese Society of Hematology]) recommends high-dose chemotherapy in combination with autologous HSCT for patients with a type of the targeted refractory or relapsed diseases if they are eligible for autologous HSCT. This indicates that Breyanzi is recommended for patients with a refractory or relapsed disease who are ineligible for autologous HSCT or who had a relapse after autologous HSCT.
- Patients with FL3B are eligible for Breyanzi treatment if they have a history of ≥2 lines of prior chemotherapy after the confirmation of FL3B, and this requirement should be clearly mentioned.

In view of the discussion at the Expert Discussion, PMDA concluded that "Indication or Performance" and "Precautions Concerning Indications or Performance" sections of Breyanzi should be modified as follows:

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed indolent non-Hodgkin lymphoma, high-grade large B-cell lymphoma

Relapsed or refractory follicular lymphoma

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen who are ineligible for autologous hematopoietic stem-cell transplantation or have a history of relapse after autologous hematopoietic stem-cell transplantation, and meet any of the following criteria:

- Patients with large B-cell lymphoma other than transformed indolent non-Hodgkin lymphoma and patients with follicular lymphoma: ≥2 lines of prior chemotherapy in the first-onset patients or ≥1 line of prior post-relapse chemotherapy in relapsed patients, which failed to achieve complete response or resulted in another relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from follicular lymphoma: a total of ≥2 lines of prior chemotherapy including ≥1 after transformation, which failed to achieve complete response or resulted in relapse.
- Patients with transformed indolent non-Hodgkin lymphoma transformed from indolent B-cell

non-Hodgkin lymphoma other than follicular lymphoma: ≥2 lines of prior chemotherapy after transformation, which failed to achieve complete response or resulted in relapse

Precautions Concerning Indications or Performance

- For follicular lymphoma, Breyanzi should be administered to patients with clinical condition of Grade 3B assessed by a well-experienced pathologist and subsequently received ≥2 lines of chemotherapy, which failed to achieve complete response or resulted in relapse.
- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on knowledge from the "Clinical Studies" section, i.e., the tissue types and prior treatment, etc. of patients enrolled in the clinical studies.

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

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.5 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be described as per the relevant sections of the Review Report (1).

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

PMDA also concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections should be described as below, with modified proposed precautions on LD chemotherapy and advice on infusion reaction associated with Breyanzi.

Dosage and Administration or Method of Use

Leukapheresis at the medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis product
   The leukapheresis product collected is packed in a refrigerated container set at 1°C to 10°C and transported to the manufacturing site of Breyanzi.

Receipt of Breyanzi at the medical institution and administration

3. Receipt and storage of Breyanzi
   Frozen Breyanzi is accepted and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before infusion
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 2 to 7 days prior to Breyanzi infusion:

Fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days, and cyclophosphamide (anhydrate) 300 mg/m^2 is infused intravenously once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).

5. Infusion of Breyanzi
   Breyanzi is thawed immediately before infusion. The usual adult dosage is a total of 100×10^6 (range, 44×10^6-100×10^6 cells) of CAR-positive viable T cells consisting of CD8-positive cells (20×10^6-50×10^6 cells) and CD4-positive cells (20×10^6-50×10^6 cells), irrespective of body weight. CD8-positive cells are first infused, followed by CD4-positive cells so that the CD8-/CD4-positive cell ratio is 1:1 (range, 0.8-1.2). Re-administration of Breyanzi is not allowed.

Precautions Concerning Dosage and Administration or Method of Use

For a series of steps from the collection of cells from the patient through the administration of Breyanzi, refer to the manufacturer's manual.

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

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

Pretreatment

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

Administration of Breyanzi

1. Check the patient identification with information on the container of Breyanzi.
2. Check the scheduled infusion timing in advance, and adjust the time to start thawing Breyanzi so that infusion can be started as soon as the patient is ready.
3. Before thawing Breyanzi, check the patient identification with information on the outer box and all vials. Thaw both the CD8-positive cell and CD4-positive cell components in vials (4 vials each at the maximum) at the same time.
4. In order to minimize the risk of infusion reaction, administer acetaminophen and diphenhydramine or another histamine H1 receptor blocker 30 to 60 minutes before the infusion of Breyanzi. Do not use corticosteroid unless a life-threatening emergency. Be prepared for emergency treatment of a severe event such as anaphylaxis following Breyanzi infusion.
5. Have ready tocilizumab (genetical recombination) for prompt use in case of emergency with cytokine release syndrome.
6. Do not use the product in case of any damage or leakage found.
7. Thaw Breyanzi completely at room temperature before infusion. Complete infusion within 2 hours after the vials are taken out of the frozen storage. Do not re-freeze thawed Breyanzi.

8. Handle separately the vial containing CD8-positive cell component and that containing CD4-positive cell component.
9. Check the volume of component indicated on the shipping certificate of each vial, and have ready syringes of a size appropriate for each vial with a patient identification label attached. Withdraw the content of each vial into each designated syringe, and confirm that the volume withdrawn is equal to that indicated in the shipping certificate.
10. Do not irradiate Breyanzi.
11. Do not use a leukocyte-removal filter for Breyanzi infusion.
12. Before infusing Breyanzi, check the patient identification with the syringe label.
13. Infuse CD8-positive cells first.
14. Infuse Breyanzi intravenously at approximately 0.5 mL/min.
15. Breyanzi contains human blood cells genetically engineered using self-inactivating lentiviral vector lacking replication competence. Discard the residual product as an infectious substance according to the rule at the medical institution.

PMDA requested the applicant to modify the “Dosage and Administration or Method of Use” and “Precautions Concerning Dosage and Administration or Method of Use” sections as described above. As the applicant appropriately responded to the request, PMDA accepted.

1.5 Post-marketing surveillance plan (draft)

At the time of application, the applicant proposed a plan of post-marketing surveillance covering all patients treated with Breyanzi to evaluate the safety, etc. of Breyanzi in clinical use. The planned sample size was 300. The planned observation period was up to 8 years.

As a result of the review in Section “7. Data Relating to Risk Analysis and Outline of the Review Conducted by PMDA” of the Review Report (1), PMDA concluded that “hypersensitivity” should be added to the safety specification of the post-marketing surveillance plan.

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

PMDA requested the applicant to modify the post-marketing surveillance plan based on the results of the Expert Discussion. In response, the applicant submitted an outline of the post-marketing surveillance plan (draft) shown in Table 63, and PMDA accepted the draft plan. The applicant explained that an initially specified item, “Administration to children,” was removed because Breyanzi is intended for adult patients and is not expected to be used in children.

Table 63. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate safety, etc., of Breyanzi in clinical use
Survey method	All-case surveillance The applicant will obtain data of the target population from the data compiled in the registry database (FormsNet) owned by the Center for International Blood and Marrow Transplant Research (CIBMTR) via the Japanese Data Center for Hematopoietic Cell Transplantation.
Population	Patients with relapsed or refractory DLBCL, PMBCL, HGBCL, tiNHL, or FL3B
Observation period	Up to 8 years
Planned sample size	300 patients
Main survey items	Safety specification CRS, nervous system events, infection, hypogammaglobulinemia, macrophage activation syndrome (hemophagocytic lymphohistiocytosis), TLS, hematocytopenia (including bone marrow failure), autoimmune disorder, aggravation of graft versus host disease, secondary carcinogenesis (including carcinogenesis due to insertional mutagenesis caused by lentiviral vector), hypersensitivity, brain edema, effect on pregnancy and breast-feeding, and long-term safety

1.6 Others

1.6.1 Designation of designated regenerative medical product

Based on “Concept for designation of biological products and specified biological products as well as designated regenerative medical products” (PFSB/ELD Notification No. 1105-1 and PFSB/MDRMPE Notification No. 1105-2 dated November 5, 2014), PMDA has concluded that Breyanzi need not be designated as a designated regenerative medical product for the following reasons:

- All human-and animal-derived components used for the manufacture of Breyanzi meet the Standard for Biological Ingredients, with a resultant extremely low risk of causing infection. MCB and WCB, which are prepared from HEK293T/17 cells and used for the manufacture of the viral vector, undergo a wide range of virus tests and are unlikely to pose any particular problem.

2. Overall Evaluation

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

Indications or Performance

The following relapsed or refractory large B-cell lymphoma:

- Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed indolent non-Hodgkin lymphoma, high-grade large B-cell lymphoma

Relapsed or refractory follicular lymphoma

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen who are ineligible for autologous hematopoietic stem-cell transplantation or have a history of relapse after autologous hematopoietic stem-cell transplantation, and meet any of the following criteria:

- Patients with large B-cell lymphoma other than transformed indolent non-Hodgkin lymphoma and

patients with follicular lymphoma: ≥2 lines of prior chemotherapy in first-onset patients or ≥1 line of prior post-relapse chemotherapy in relapsed patients, which failed to achieve complete response or resulted in another relapse

- Patients with transformed indolent non-Hodgkin lymphoma transformed from follicular lymphoma: a total of ≥2 lines of prior chemotherapy including ≥1 after transformation, which failed to achieve complete response or resulted in relapse
- Patients with transformed indolent non-Hodgkin lymphoma transformed from indolent B-cell non-Hodgkin lymphoma other than follicular lymphoma: ≥2 lines of prior chemotherapy after transformation, which failed to achieve complete response or resulted in relapse

Dosage and Administration or Method of Use

Leukapheresis at the medical institution and transportation to the manufacturing site

1. Leukapheresis
   Non-mobilized peripheral blood mononuclear cells are collected by leukapheresis.
2. Transportation of leukapheresis product
   The leukapheresis product collected is packed in a refrigerated container set at 1°C to 10°C and transported to the manufacturing site of Breyanzi.

Receipt of Breyanzi at the medical institution and administration

3. Receipt and storage of Breyanzi
   Frozen Breyanzi is accepted and cryopreserved in the vapor phase of liquid nitrogen (≤−130°C) until immediately before use.
4. Pretreatment before infusion
   The patient undergoes a blood test, etc. for condition checking and receives the following lymphodepleting chemotherapy from 2 to 7 days prior to Breyanzi infusion:
   Fludarabine phosphate 30 mg/m^2 is infused intravenously once daily for 3 days, and cyclophosphamide (anhydrate) 300 mg/m^2 is infused intravenously once daily for 3 days. The doses may be reduced depending on the patient's condition (e.g., renal impairment).
5. Infusion of Breyanzi
   Breyanzi is thawed immediately before infusion. The usual adult dosage is a total of 100×10^6 (range, 44×10^6-100×10^6 cells) of CAR-positive viable T cells consisting of CD8-positive cells (20×10^6-50×10^6 cells) and CD4-positive cells (20×10^6-50×10^6 cells), irrespective of body weight. CD8-positive cells are first infused, followed by CD4-positive cells so that the CD8-/CD4-positive cell ratio is 1:1 (range, 0.8-1.2). Re-administration of Breyanzi is not allowed.

Approval Conditions

1. The applicant is required to ensure that the product is used at medical institutions well-equipped for handling emergencies and prepared for appropriate measures including the management of cytokine release syndrome, under the supervision of a physician with sufficient knowledge and experience in treatment of hematopoietic malignancies and hematopoietic stem cell transplantation.
2. Because only a limited number of Japanese patients participated in the clinical studies of the product, the applicant is required to conduct a use-results survey covering all Japanese patients

treated with the product in the post-marketing setting, until data from a certain number of cases are collected, in order to identify the characteristics of patients using the product and promptly collect safety and efficacy data, and thereby to take necessary measures to ensure the proper use of the product.

Appendix

List of Abbreviations

Anti-CD19 CAR	anti-CD19 chimeric antigen receptor
AP	activator protein
Application	Application for marketing approval
ATCC	American Type Culture Collection
AUC_{0-28}	Area under the concentration-time curve through 28 days after infusion
BAV	bovine adenovirus
BCMA	B-cell maturation antigen
BPV	bovine parvovirus
Breyanzi	Breyanzi for intravenous injection
BRSV	bovine respiratory syncytial virus
BSA	bovine serum albumin
BTV	bluetongue virus
[redacted] cell	[redacted] cell
BVDV	bovine viral diarrhea virus
CAR	chimeric antigen receptor
CD	cluster of differentiation
Cetuximab	Cetuximab (Genetical Recombination)
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	Maximum observed concentration
CMV	cytomegalovirus
Component cells	cells serving as a component of the product
CPE	cytopathic effect
CQA	critical quality attribute
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EBV	Epstein-Barr virus
ECOG PS	Eastern Cooperative Oncology Group performance status
[redacted]	[redacted]
EGFRt	Truncated epidermal growth factor receptor
EOP	end of production cell
FBS	fetal bovine serum
FL3B	follicular lymphoma grade 3B
Fludarabine	Fludarabine Phosphate
FMC63 scFv	single-chain variable region derived from anti-CD19 murine monoclonal antibody (mouse hybridoma strain FMC63)
FN	febrile neutropenia
GC	genome copy
HAD	haemadsorption
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HEK293T/17 cells	human embryonic kidney cells 293T/17
HEV	hepatitis E virus
HGBCL	high grade B-cell lymphoma
HHV	human herpes virus

HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
HSV	herpes simplex virus
HTLV	human T-cell leukemia virus
IBRV	Infectious bovine rhinotracheitis virus
ICU	intensive care unit
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHC	immunohistochemistry
iiNT	investigator-identified neurotoxicity
IL	interleukin
Juno Inc.	Juno Therapeutics, Inc.
K562 cells	human chronic myeloid leukemia cells
LD chemotherapy	Lymphodepleting chemotherapy
LTR	long terminal repeat
MCB	master cell bank
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
[redacted]	[redacted]
MRC-5 cells	human fetal lung fibroblasts
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas
NFAT	nuclear factor of activated T-cells
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NHP	non-human primate
NK cell	natural killer cell
NKT cell	natural killer T cell
Nur77	nuclear hormone receptor-77
OS	overall survival
PAS	Primary analysis set
PAV	porcine adenovirus
PBMC	peripheral blood mononuclear cell
PCNSL	Primary DLBCL of the CNS
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PI3	parainfluenza-3
PMBCL	primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	porcine parvovirus
PR	partial response
PT	preferred term
PVB19	human parvovirus B19
QbD	quality by design
qPCR	quantitative polymerase chain reaction
[redacted]	[redacted]
RABV	rabies virus
RCL	replication competent lentivirus
REO	reo virus
RRE	Rev-responsive element
scFv	single-chain variable fragment
SD	stable disease

SMQ	standardised MedDRA queries
Study BCM-001	Study JCAR017-BCM-001
SV40	simian virus 40
TFL	transformed follicular lymphoma
TGEV	transmissible gastroenteritis virus
tiNHL	transformed indolent non-Hodgkin lymphoma
TLS	tumor lysis syndrome
t_{max}	Time to maximum observed concentration
TNF	tumor necrosis factor
Tocilizumab	Tocilizumab (Genetical Recombination)
TSE	transmissible spongiform encephalopathy
Vero cells	African green monkey kidney epithelial cells
VSV-G	glycoprotein of the vesicular stomatitis virus
WCB	working cell bank
WHO	World Health Organization