December 12, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products, 1. Human Somatic Cell Processed Product
Non-proprietary Name	Lisocabtagene maraleucel
Brand Name	Breyanzi Suspension for Intravenous Infusion
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 25, 2022 (Application for partial change approval)

Results of Deliberation

In the meeting held on December 12, 2022, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved. The re-examination period for the present application is the remainder of re-examination period for the initial approval (until March 21, 2031).

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

November 24, 2022
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Breyanzi Suspension for Intravenous Infusion
Classification	Human Cellular/Tissue-based Products, 1. Human Somatic Cell Processed Product
Non-proprietary Name	Lisocabtagene maraleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 25, 2022

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	(3) Regenerative medical product with new indications
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 efficacy in the treatment of relapsed or refractory large B-cell lymphoma and relapsed or refractory follicular lymphoma after 1 line of prior therapy with the product, 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 types of 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~~

(Underline denotes additions. Strike-through denotes deletions.)

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.

(No change)

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)

September 16, 2022

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

Product Submitted for Approval

Brand Name	Breyanzi Suspension for Intravenous Infusion
Classification	Human Cellular/Tissue-based Products, 1. Human Somatic Cell Processed Product
Non-proprietary Name	Lisocabtagene maraleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 25, 2022

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 Indications or Performance

The following types of 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, T-cell/histiocyte-rich 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~~

(Underline denotes additions. Strike-through denotes deletions.)

Proposed 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.

(No change)

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-positive 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.

In Japan, Breyanzi was approved in March 2021 for the treatment of relapsed or refractory large B-cell lymphoma (LBCL) (diffuse large B-cell lymphoma [DLBCL], primary mediastinal large B-cell lymphoma [PMBCL], transformed indolent non-Hodgkin lymphoma (tiNHL), and high grade B-cell lymphoma [HGBCL]) and follicular lymphoma grade 3B (FL3B) after ≥2 lines of prior therapy.

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.

For the clinical development of Breyanzi for the treatment of LBCL or FL3B, the applicant initiated a global phase III study (Study JCAR017- BCM-003 [Study BCM-003]) in October 2018. This study involved patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who were eligible for autologous hematopoietic stem cell transplant (HSCT). The applicant also started a global phase II study (Study JCAR017- BCM-001 [Study BCM-001]) Cohort 2 and a foreign phase II study (Study 017006) in [redacted] and July 2018, respectively. Both studies involved patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who were ineligible for autologous HSCT.

In the US, an application for marketing approval of Breyanzi was submitted in December 2021 with the results from Studies BCM-003 and 017006 as pivotal data. In June 2022, Breyanzi was approved for the following indications or performance.

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.

In Europe, an application for marketing approval of Breyanzi was submitted in [redacted] 2022 with the results from Study BCM-003 as pivotal data, and is under review as of September 2022.

A partial change application for Breyanzi was submitted to add the indications or performance for relapsed or refractory LBCL or FL3B after 1 line of prior therapy, based on the results of Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006.

2. Quality and Outline of the Review Conducted by PMDA

The present application is intended for the new indication, and no data relating to quality were submitted.

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

Although the present application is intended for the new indication, no new data were submitted because the data relating to primary pharmacodynamics or performance had been evaluated during the review of the initial application.

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

Th present application is intended for the new indication, and no data relating to non-clinical safety were submitted.

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

The applicant submitted data on the biological disposition of Breyanzi obtained in Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006. However, the results were confirmed to be similar to those submitted in the initial application.

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

The applicant submitted efficacy and safety evaluation data from 3 clinical studies (1 each of global phase III study, global phase II study, and foreign phase II study), as shown in Table 1.

Table 1. List of clinical studies for efficacy and safety

Data category	Region	Study identifier	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Global	BCM-003	III	Patients with relapsed or refractory aggressive B-cell NHL who are eligible for autologous HSCT	184 (a) 92 (b) 92	(a) Breyanzi A single intravenous dose of 100×10^6 anti-CD19 CAR T cells (b) Standard therapy Three cycles of salvage chemotherapy (3 weeks in each cycle), followed by HDCT in combination with autologous HSCT if subjects were responsive to the salvage therapy	Efficacy Safety
	Global	BCM-001 (Cohort 2)	II	Patients with relapsed or refractory aggressive B-cell NHL who are ineligible for autologous HSCT	31	A single intravenous dose of 100×10^6 anti-CD19 CAR T cells	Efficacy Safety
	Foreign	017006	II	Patients with relapsed or refractory aggressive B-cell NHL who are ineligible for autologous HSCT	74	A single intravenous dose of 100×10^6 anti-CD19 CAR T cells	Efficacy Safety

Each clinical study is summarized in the following sections. The most common adverse events other than death observed in each clinical study are presented in Section "8. Adverse Events Observed in Clinical Studies."

6.1 Evaluation data

6.1.1 Global studies

6.1.1.1 Global phase III study (CTD 5.3.5.1.1; Study BCM-003, ongoing since October 2018 [data cut-off on March 8, 2021])

An open-label, randomized study was conducted at 53 study sites in 11 countries including Japan to investigate the efficacy and safety of Breyanzi versus the standard therapy in patients with relapsed or refractory aggressive B cell non-Hodgkin lymphoma (NHL) who were eligible for autologous HSCT (target sample size,[1)] 182 patients [91 in each treatment group]). Table 2 shows the main inclusion/exclusion criteria.

1) Assuming that the hazard ratio of EFS, the primary endpoint, in the Breyanzi group to the standard therapy group is 0.55, the number of events necessary to provide 90% statistical power with a one-sided significance level of 2.5% was determined to be 119, and the number of subjects required to achieve the target event number was determined to be 182 (91 in each group).

Table 2. Main inclusion/exclusion criteria

Inclusion criteria • Patients histologically diagnosed with B cell NHL of any of the following subtypes according to the WHO classification (2016) (*Blood.* 2016;127:2375-90): ➢ DLBCL NOS (*de novo* or tiNHL) ➢ HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology ➢ PMBCL ➢ THRLBCL ➢ FL3B • Patients with refractory disease (PD, SD, PR, or CR with relapse before 3 months) or relapsed disease (defined as CR lasting at least 3 months but not more than 12 months) after 1 line of prior chemotherapy containing CD20-targeted agent and an anthracycline • Patients with the Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 Exclusion criteria • Patients ineligible for autologous HSCT • Patients who received a prior gene therapy product or previous CD19-targeted therapy • Patients with primary cutaneous LBCL, Epstein-Barr virus-positive DLBCL, Burkitt's lymphoma, or Richter transformation from CLL or small lymphocytic lymphoma

The study consisted of screening (from screening to randomization of leukapheresed subjects to the Breyanzi group or the standard therapy group), treatment period (from Days 0 to 126 after randomization), post-treatment follow-up period (from Day 127 to Month 36 after randomization), and survival follow-up period (from Month 37 after randomization onward).

The dosage regimen or method of use of Breyanzi in the Breyanzi group was as follows: 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells) were infused intravenously as a single dose on Day 29 after randomization. In order to facilitate the engraftment and growth of Breyanzi in the body, Breyanzi infusion was preceded by treatment with lymphodepleting chemotherapy ("LD chemotherapy") consisting of an intravenous infusion of cyclophosphamide hydrate ("cyclophosphamide") 300 mg/m^2 and fludarabine phosphate ("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 bridging chemotherapy for disease control. Bridging chemotherapy was one[2)] of the salvage therapies (R-DHAP,[3)] R-ICE,[4)] and R-GDP[5)]) used in the standard therapy group and had to be completed ≥7 days before the start of LD chemotherapy.

In the standard therapy group, one of the salvage chemotherapies (R-DHAP, R-ICE, and R-GDP) was selected as per the investigator and given in 3 cycles (3 weeks for each cycle) starting from Day 1 after randomization. Peripheral hematopoietic stem cells for autologous HSCT were harvested during the salvage chemotherapy. Subjects who showed response to the 3 cycles of salvage chemotherapy received high-dose chemotherapy (HDCT)[6)] in combination with autologous HSCT. Subjects in the standard therapy group were allowed to crossover to receive Breyanzi if they were confirmed to meet one of the

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2) Of 92 subjects randomized to the Breyanzi group, 58 received bridging chemotherapy. The most used chemotherapy was R-ICE (29 subjects).

3) Intravenous administration of rituximab 375 mg/m^2 on Day 1, dexamethasone 40 mg on Days 1 to 4, cytarabine 2,000 mg/m^2 twice daily on Day 2, and cisplatin 100 mg/m^2 on Day 1.

4) Intravenous administration of rituximab 375 mg/m^2 on Day 1, ifosfamide 5,000 mg/m^2 on Day 2, etoposide 100 mg/m^2 on Days 1 to 3, and carboplatin AUC5 (maximum dose of 800 mg) on Day 2.

5) Intravenous administration of rituximab 375 mg/m^2 on Day 1, dexamethasone 40 mg on Days 1 to 4, gemcitabine 1,000 mg/m^2 on Days 1 and 8, and cisplatin 75 mg/m^2 on Day 1.

6) The standard HDCT consisted of intravenous administration of carmustine (BCNU) 300 mg/m^2 on Day 1, etoposide 200 mg/m^2 on Days 2 to 5, cytarabine 200 mg/m^2 on Days 2 to 5, and melphalan 140 mg/m^2 on Day 6. In Japan where intravenous BCNU is unavailable for use, ranimustine (MCNU) was used in its stead according to the same dosage regimen and schedule as that of BCNU.

following criteria by the Independent Response Committee (IRC), upon the request of the investigator. Subjects who crossed over to receive Breyanzi were followed up for 12 months after Breyanzi infusion.

- Failure to achieve complete response (CR) or partial response (PR) by 9 weeks post-randomization (after 3 cycles of salvage chemotherapy)
- Progressive disease (PD) at any time
- Need to start a new anticancer therapy due to efficacy concerns after ≥18 weeks post-randomization

The primary endpoint was event-free survival (defined as time from the day of randomization to death from any cause, PD, failure to achieve CR/PR by 9 weeks post-randomization, or start of a new anticancer therapy due to efficacy concerns, whichever occurred first; hereinafter referred to as "EFS") assessed by the IRC according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68).

Initially, one interim analysis had been planned[7)] to terminate the study early for efficacy, which was to be conducted at 60% information fraction where approximately 71 EFS events were confirmed (the first interim efficacy analysis). The independent data monitoring committee conducted the first interim efficacy analysis on [redacted] (data cut-off date for the first interim efficacy analysis, [redacted]), and reported [redacted] because [redacted]. Taking into account that [redacted], the [redacted] was revised ([redacted]) to conduct the second interim efficacy analysis at 80% information fraction where approximately 95 EFS events were confirmed. The information related to the series of the discussion was not disclosed to the clinical development personnel of the sponsor to maintain blindness.

At the second interim efficacy analysis (data cut-off on March 8, 2021), all of the 184 subjects who had undergone leukapheresis after enrollment were randomized to either of the treatment groups (92 in the Breyanzi group, 92 in the standard therapy group, including 5 and 4 Japanese subjects, respectively). In the Breyanzi group, 90 subjects received Breyanzi and the remaining 2 subjects discontinued the study before the start of LD chemotherapy (due to consent withdrawal and manufacturing failure). A total of 89 subjects received Breyanzi that met the release specifications while 1 subject received the off-specification product. In the standard therapy group, 91 subjects received salvage chemotherapy, and the remaining 1 subject discontinued the study due to consent withdrawn before the start of salvage chemotherapy. Of the 91 subjects receiving salvage chemotherapy, 43 received HDCT. Of them, 42 subjects received autologous HSCT after completing HDCT, but the remaining 1 subject had yet to undergo autologous HSCT at the data cut-off time point. A total of 50 subjects in the standard therapy group were approved to crossover to receive Breyanzi. Of them, 47 subjects received Breyanzi infusion, but 3 subjects did not (2 fatal cases and 1 who had yet to receive Breyanzi at the data cut-off time point). Of those who crossed over to receive Breyanzi, 46 subjects received Breyanzi that met the release specifications while the remaining 1 subject received the off-specification product. The efficacy analysis

7) O'Brien-Fleming α-spending function was used to adjust for the multiplicity of hypothesis testing in the first interim analysis for efficacy. The null-hypothesis was to be rejected if one-sided *P* value was ≤0.005.

set included 184 randomized subjects (92 in the Breyanzi group and 92 in the standard therapy group, including 5 and 4 Japanese subjects, respectively). The safety analysis set included 92 subjects who were randomized to the Breyanzi group and received the study treatment and 91 subjects who were randomized to the standard therapy group and received salvage chemotherapy as the standard therapy (including 5 Japanese subjects in the Breyanzi group and 4 Japanese subjects in the standard therapy group).

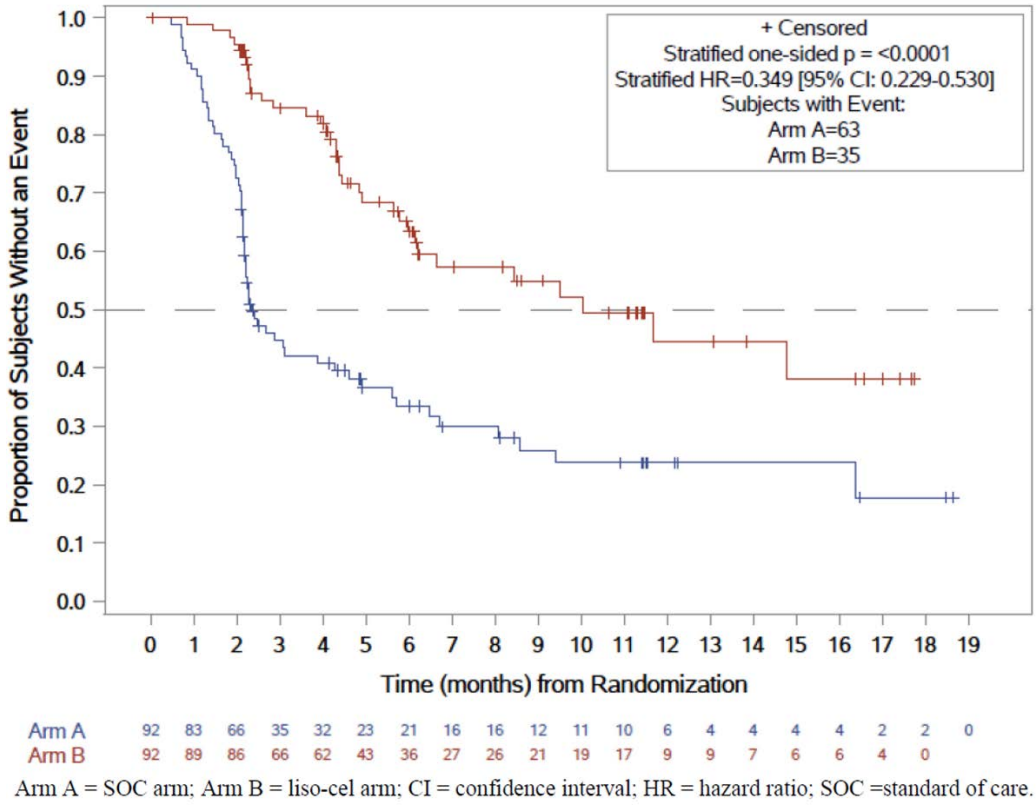
Results of the primary endpoint EFS and the Kaplan-Meier curves at the second interim efficacy analysis (data cut-off on March 8, 2021) are shown in Table 3 and Figure 1, respectively, demonstrating the superiority of Breyanzi to the standard therapy (one-sided *P* value <0.0001, stratified Cox proportional hazard model).

Table 3. Results of the second interim analysis on EFS (IRC assessment, efficacy analysis set, data cut-off on March 8, 2021)

	Breyanzi N = 92	Standard therapy N = 92
EFS events (%)	35 (38.0)	63 (68.5)
Death (%)	2 (2.2)	2 (2.2)
PD (%)	26 (28.3)	39 (42.4)
Failure to achieve CR/PR by 9 weeks post-randomization (%)	4 (4.3)	17 (18.5)
Start of a new anticancer therapy due to efficacy concerns (%)	3 (3.3)	5 (5.4)
Median [95% CI] (months)	10.1 [6.1, NE]	2.3 [2.2, 4.3]
Hazard ratio [95% CI][*1]	0.349 [0.229, 0.530]	
One-sided *P* value[*1,*2]	<0.0001	

*1 Calculated by stratified Cox proportional hazard model with initial therapeutic effect (PD, stable disease [SD], PR, or CR with relapse before 3 months; or relapse after CR lasting at least 3 months) and second-line age-adjusted international prognostic index (sAAIPI) (0 or 1 vs. 2 or 3) as the stratification factors.

*2 Significance level of 0.012 (one-sided). O'Brien-Fleming α-spending function was used to adjust for the multiplicity of hypothesis testing in the interim analysis. Alpha-spending in the first interim efficacy analysis was taken into account for the calculation of the significance level.



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; SOC =standard of care.

Figure 1. Kaplan-Meier curves of EFS in Study BCM-003 (efficacy analysis set, data cut-off on March 8, 2021)

Death occurred in 20 subjects (12 in the Breyanzi group, 8 in the standard therapy group) during the treatment period and the post-treatment follow-up period combined. Disease progression occurred in 11 subjects (7 in the Breyanzi group, 4 in the standard therapy group) and death due to adverse events[8)] occurred in 3 subjects (1 in the Breyanzi group, 2 in the standard therapy group). Six subjects (4 in the Breyanzi group, 2 in the standard therapy group) died outside of the period of adverse event collection. The cases of death due to adverse events were assessed. One subject in the Breyanzi group died due to failure to thrive[9)] 45 days after infusion, but the death was considered unrelated to Breyanzi. In both subjects in the standard therapy group (sepsis that occurred after HDCT and acute respiratory distress syndrome in 1 subject each), the cases of death were considered unrelated to the standard therapy.

8) In the Breyanzi group, only adverse events occurring or worsening within 90 days after randomization were assessed. In the standard therapy group, adverse events occurring or worsening within 90 days after the last dose of salvage chemotherapy after randomization or those occurring at ≥91 days after the last dose and suspected to be causally related to the study treatment were collected for assessment. Adverse events occurring after the start of a new anticancer therapy were not subjected to assessment.

9) A 7[redacted]-year-old man with the primary disease of HGBCL. The subject received R-GDP therapy (9-16 days post-randomization), followed by Breyanzi infusion (50.74×10^6 CD8-positive T cells, 49.17×10^6 CD4-positive T cells) 35 days post-randomization. The subject showed disease progression 35 days after Breyanzi infusion (corresponding to 69 days post-randomization) and died 45 days after Breyanzi infusion (79 days post-randomization). Autopsy was not performed. The death was considered to be "failure to thrive" because the subject showed progressive decline in physical and cognitive function. At the time point of randomization, the subject had complications such as glaucoma, cataract, bilateral hearing loss, benign prostatic hyperplasia, bradycardia, haemorrhagic diathesis, appetite disorder, dysuria, and back pain, but no complication related to the cause of death was reported. The subject experienced the following blood cell disorders: Leukopenia (Grade 2-4) from the next day of Breyanzi infusion (36 days post-randomization) up to 43 days after Breyanzi infusion, neutropenia (Grade 4) from 17 to 45 days after Breyanzi infusion, thrombocytopenia (Grade 3-4) from 13 to 43 days after Breyanzi infusion, and anaemia (Grade 2) from before Breyanzi infusion up to 43 days after Breyanzi infusion.

6.1.1.2 Global phase II study (CTD 5.3.5.2.2, Cohort 2 of Study BCM-001 [ongoing since [redacted] 20[redacted] (data cut-off on March 2, 2022)])

A multi-cohort, open-label, uncontrolled study was conducted to investigate the efficacy and safety of Breyanzi in patients with aggressive B cell NHL. Patients with relapsed or refractory aggressive B cell NHL ineligible for autologous HSCT (target sample size, 28 patients[10)]) were enrolled in Cohort 2 (conducted at 13 study sites in 10 countries including Japan). Table 4 shows the main inclusion/exclusion criteria in Cohort 2 of Study BCM-001.

Table 4. Main inclusion/exclusion criteria

Inclusion criteria • Patients histologically diagnosed with B cell NHL of any of the following types according to the WHO classification (2016) (*Blood.* 2016;127:2375-90): ➢ DLBCL NOS (*de novo* or transformed from FL) ➢ HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology ➢ FL3B • Patients with 1 line of prior chemotherapy including CD20-targeted agent and anthracycline • Patients ineligible for autologous HSCT • Patients with ECOG PS score of 0 to 2 Exclusion criteria • Patients who received treatment with a prior gene therapy product or previous CD19-targeted therapy

The study consisted of the pre-treatment period (after screening, from leukapheresis to the start of LD chemotherapy, and during Breyanzi manufacturing), treatment period (from the start of LD chemotherapy to Day 29 after Breyanzi infusion), and post-treatment follow-up (from Day 30 after Breyanzi infusion to Month 24 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 pretreatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 once daily and fludarabine 30 mg/m^2 once daily for 3 days. Breyanzi was to be 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 bridging chemotherapy for disease control. The bridging chemotherapy was to be performed with a low-dose anticancer drug (e.g., vincristine, rituximab, and cyclophosphamide ≤300 mg/m^2/day) and had to be completed ≥7 days before the start of LD chemotherapy. Patients underwent pre-LD chemotherapy assessment for positron emission tomography (PET)-positivity after bridging chemotherapy. Patients had to meet the relevant criteria before LD chemotherapy and Breyanzi infusion.

Of 35 patients (including 4 Japanese patients) who underwent screening, 32 patients[11)] (including 3 Japanese patients) were enrolled in the study and underwent leukapheresis. Of them, 5 discontinued the study before Breyanzi infusion (3 died and 2 [including 1 Japanese patient] failed to meet the criteria for Breyanzi infusion although they met the inclusion/exclusion criteria at screening), and 27 patients[11)]

10) Assuming the target overall response rate (the primary endpoint) of 70%, the number of subjects necessary to provide 80% statistical power was determined to be 28 at the threshold level of 40% and one-sided significance level of 2.5%.

11) One subject was found not to meet the inclusion/exclusion criteria after Breyanzi infusion, but was included in the efficacy and safety analysis sets.

(including 2 Japanese patients) received Breyanzi that met the release specifications. The patients receiving Breyanzi were included in the efficacy and safety analysis sets.

The primary efficacy endpoint was the overall response rate assessed by the IRC according to the Lugano response criteria (*J Clin Oncol.* 2014;32:3059-68). The threshold response rate, which had been 40%[12] at the start of the study, was changed to 50.2% based on the results[13] from patients with relapsed or refractory aggressive B cell NHL obtained later in clinical settings (protocol amendment, ver. [redacted]).

Table 5 shows the results of the overall response rate by IRC assessment according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68), the primary endpoint. There was no statistically significant difference from the pre-specified threshold (50.2%) (one-sided *P* value = 0.128, exact binomial test).

Table 5. Best response (IRC assessment, efficacy analysis set, data cut-off on March 2, 2022)

	n (%)
	N = 27
CR	13 (48.1)
PR	4 (14.8)
SD	3 (11.1)
PD	6 (22.2)
Not evaluated	1 (3.7)
Complete response (CR)	13
Complete response rate [95% CI[*1]] (%)	48.1 [28.7, 68.1]
Response (CR or PR)	17
Overall response rate [95% CI[*1]] (%)	63.0 [42.4, 80.6]
One-sided *P* value[*2]	0.128

*1 Clopper-Pearson method
*2 Exact binomial test for significance level of 0.025 (one-sided) and threshold response rate of 50.2%

Death occurred in 12 subjects within 24 months after Breyanzi infusion. Eleven subjects died due to disease progression and 1 subject due to adverse event[14] (haemophagocytic lymphohistiocytosis).[15] A causal relationship to Breyanzi could not be ruled out for the death caused by the adverse event (haemophagocytic lymphohistiocytosis).

12) The value was defined by taking account of the meta-analysis using the results of studies on therapies recommended for patients with relapsed or refractory DLBCL (*Blood.* 2015;125:1394-402, *Haematologica.* 2013;98:1726-31, etc.) and the results of preliminary analysis of data from Study 017001.

13) A retrospective observational study (NDS-NHL-001) was conducted to obtain data on the treatment of relapsed or refractory aggressive B cell NHL in clinical settings. For this purpose, post-treatment data were collected from patients with relapsed or refractory aggressive B cell NHL after 1 line of prior chemotherapy including CD20-targeted drug and anthracycline, who were diagnosed with diffuse large B-cell lymphoma, Not otherwise specified (DLBCL NOS) (*de novo* or transformed follicular lymphoma [tFL]), HGBCL, or FL3B in or after 2003 in Japan, the US, or Europe. Of 601 patients from whom data were collected, 273 patients had similar baseline clinical conditions as those who were enrolled in Study 017006 and were ineligible for HSCT, and the overall response rate in these patients was 50.2% (data cut-off on [redacted]).

14) Events occurring within 90 days after Breyanzi infusion were assessed. Events occurring after the start of a new anticancer therapy were not included in the assessment.

15) A 7[redacted]-year-old woman with the primary disease of DLBCL NOS. The subject had Grade 2 cytokine release syndrome (CRS) and neurotoxicity (Grade 1 encephalopathy) 2 days after Breyanzi infusion and serious cardiac failure (Grade 3) 3 days after infusion, and remained hospitalized even after improvement in these symptoms to receive treatment with steroid, tocilizumab (genetical recombination), diuretics, etc. At 25 days after infusion, she had gastric haemorrhage (Grade 4) and was transferred to intensive care unit (ICU), received blood transfusion and other treatments which led to improvement. She had urinary tract infection (Grade 3) 36 days after infusion, and gastric haemorrhage (Grade 3) 37 days after infusion, resulting in transfer to ICU. She had hemophagocytic syndrome (Grade 4) 39 days after infusion, and died 50 days after infusion.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase II study (CTD 5.3.5.2.1, Study 017006 [ongoing since July 2018 (data cut-off on September 24, 2021)])

An open-label, uncontrolled study was conducted at 23 study sites in the US to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory aggressive B cell NHL who were ineligible for autologous HSCT (target sample size, 62 patients[16)]). Table 6 shows main inclusion/exclusion criteria.

Table 6. Main inclusion/exclusion criteria

Inclusion criteria • Patients histologically diagnosed with B cell NHL of any of the following types according to the WHO classification (2016) (*Blood.* 2016;127:2375-90): ➢ DLBCL NOS (*de novo* or transformed from FL) ➢ HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology ➢ FL3B • Patients with 1 line of prior chemotherapy including anthracycline and rituximab (or other CD20-targeted drugs) • Patients with ECOG PS score of 0 to 2 • Patients ineligible for autologous HSCT Exclusion criteria • Patients who received previous CD19-targeted therapy

The study consisted of the pre-treatment period (after screening, from leukapheresis through LD chemotherapy, and during Breyanzi manufacturing), treatment period (from the start of LD chemotherapy through Day 29 of Breyanzi infusion), and post-treatment follow-up period (from Day 30 after Breyanzi infusion to Month 24 after Breyanzi infusion).

In order to facilitate the engraftment and growth of Breyanzi in the body, Breyanzi infusion was preceded by pretreatment with LD chemotherapy consisting of an intravenous infusion of cyclophosphamide 300 mg/m^2 once daily 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 anticancer therapy for disease control (bridging chemotherapy). The bridging chemotherapy was to be performed with a low-dose anti-cancer agent (e.g., cyclophosphamide ≤300 mg/m^2/day) and had to be completed ≥7 days before the start of LD chemotherapy.

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).

Of 93 patients who underwent screening, 74 (including 1 who was later found to be ineligible) were enrolled and underwent leukapheresis. After leukapheresis, 12 subjects discontinued the study (death due to disease progression in 5 subjects, disease-associated complication in 1 subject, failure to meet inclusion/exclusion criteria in 5 subjects, expiration of shelf-life due to postponement of Breyanzi infusion in 1 subject), 61 subjects received Breyanzi that met the release specifications, and 1 subject received the off-specification product. All of the 61 subjects who received Breyanzi infusion were included in the primary efficacy and safety analysis sets.

16) Assuming the target overall response rate (the primary endpoint) of 70%, the number of subjects necessary to provide 85% statistical power was determined to be 62 at the threshold level of 50% and one-sided significance level of 2.5%.

The primary efficacy endpoint was the overall response rate assessed by the IRC according to the Lugano response criteria (*J Clin Oncol.* 2014;32:3059-68). The threshold response rate, which had been 50%[17] at the start of the study, was changed to 50.2% based on the results[13] from patients with relapsed or refractory aggressive B cell NHL obtained later in clinical settings (protocol amendment, ver. [redacted], [redacted], 20[redacted]).

Table 7 shows the results of the overall response rate by IRC assessment according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68), the primary endpoint. The observed difference met the pre-specified threshold (50.2%) for statistical significance (one-sided *P* value <0.0001, exact binomial test).

Table 7. Best response (IRC assessment, efficacy analysis set, data cut-off on September 24, 2021)

	n (%)
	N = 61
CR	33 (54.1)
PR	16 (26.2)
SD	3 (4.9)
PD	8 (13.1)
Not evaluated	1 (1.6)
Complete response (CR)	33
Complete response rate [95% CI*1] (%)	54.1 [40.8, 66.9]
Response (CR or PR)	49
Overall response rate [95% CI*1] (%)	80.3 [68.2, 89.4]
One-sided *P* value*2	<0.0001

*1 Clopper-Pearson method
*2 Exact binomial test for significance level of 0.025 (one-sided) and threshold response rate of 50.2%

Death occurred in 21 subjects within 24 months after Breyanzi infusion. Seventeen subjects died due to disease progression, 2 subjects due to adverse events[14] other than disease progression (coronavirus disease [COVID-19][18] and COVID-19 pneumonia[19] in 1 subject each), and 2 subjects due to other reason (death not included in adverse events). A causal relationship to Breyanzi could not be ruled out for COVID-19 in 1 subject.

6.R Outline of the review conducted by PMDA

6.R.1 Data for review

PMDA determined that, among the evaluation data submitted, Study BCM-003 in patients eligible for autologous HSCT was important in evaluating the efficacy and safety of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy. The efficacy and safety evaluation primarily focused on these data. The efficacy and safety of Breyanzi in patients ineligible for autologous HSCT was investigated based on the results of Cohort 2 of Study BCM-001 and Study 017006, both involving patients ineligible for autologous HSCT.

17) Determined based on the results of the meta-analysis using the data of the second-line therapy recommended for patients with relapsed or refractory aggressive B cell NHL (*Haematologica.* 2013;98:1726-31, etc.).

18) A 6[redacted]-year-old man with primary disease of DLBCL NOS. The subject had neurotoxicity (Grade 1 disturbance in attention) and COVID-19 (Grade 4) 12 days and 15 days, respectively, after Breyanzi infusion. He was hospitalized due to pyrexia, dyspnoea and other conditions 18 days after infusion. Because the symptoms improved after treatment with dexamethasone, remdesivir, etc., the subject was discharged 22 days after infusion. However, he was re-hospitalized 33 days after infusion because of worsening of respiratory conditions. Treatment with dexamethasone, remdesivir, etc., did not improve the symptom and the subject died 63 days after infusion.

19) An 8[redacted]-year-old man with the primary disease of HGBCL. The subject had cough, dyspnea, etc., 37 days after Breyanzi infusion, and was emergency admitted and diagnosed with COVID-19 pneumonia (Grade 4) 38 days after infusion. He was found to have had bacteraemia (Grade 4) and respiratory distress syndrome (Grade 4), and was hospitalized. Treatment with antibacterials, antiviral agents, antibody drugs, etc., did not improve the symptoms. It was decided not to control with mechanical ventilation, and the subject died 43 days after infusion.

The efficacy and safety of Breyanzi in Japanese patients were investigated based on the data from Study BCM-003 and Cohort 2 of Study BCM-001.

6.R.2 Efficacy

As a result of the review presented in the subsections below, PMDA has concluded that Breyanzi was shown to have efficacy in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

6.R.2.1 Control group

The applicant's explanation about the justification for the control group used in Study BCM-003:

For the treatment of patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are eligible for autologous HSCT, the Japanese and foreign clinical practice guidelines recommend the use of platinum-based salvage chemotherapy (R-DHAP, R-ICE, R-GDP, etc.) and, if patients have response to the treatment, proceeding to HDCT in combination with autologous HSCT. Accordingly, the above recommended therapy was employed in the standard therapy group (control group) in Study BCM-003.

PMDA accepted the explanation of the applicant.

6.R.2.2 Efficacy endpoint

The applicant's explanation about the reason for using IRC-assessed EFS as the primary endpoint in Study BCM-003:

EFS was defined as time from randomization to death, PD, failure to achieve CR/PR by 9 weeks post-randomization, or start of a new anticancer chemotherapy due to efficacy concerns, whichever occurred first. In the treatment of patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are eligible for autologous HSCT, if patients do not respond to salvage chemotherapy, it is recommended to immediately start a new anticancer therapy instead of administering HDCT in combination with autologous HSCT. The start of the new chemotherapy is an event corresponding to failure of second-line therapy. In clinical studies in this patient population, those without response to the salvage chemotherapy had a poorer prognosis than those with response (*J Clin Oncol.* 2010;28:4184-90, *J Clin Oncol.* 2017;35:544-51, etc.). These findings suggest that improvement in EFS in the Breyanzi group versus the standard therapy group is of clinical significance in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy, warranting the use of EFS as the primary endpoint.

PMDA's view:

The applicant's explanation is generally understandable. However, progression free survival (PFS) and overall survival (OS) are also important in evaluating the treatment efficacy in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are eligible for autologous HSCT. For this reason, the efficacy of Breyanzi is evaluated based not only on EFS assessed by the IRC, the primary endpoint, but also on PFS and OS.

6.R.2.3 Results of efficacy evaluation

The applicant's explanation about the efficacy of Breyanzi in patients with relapsed or refractory LBCL after1 line of prior therapy who are eligible for autologous HSCT:

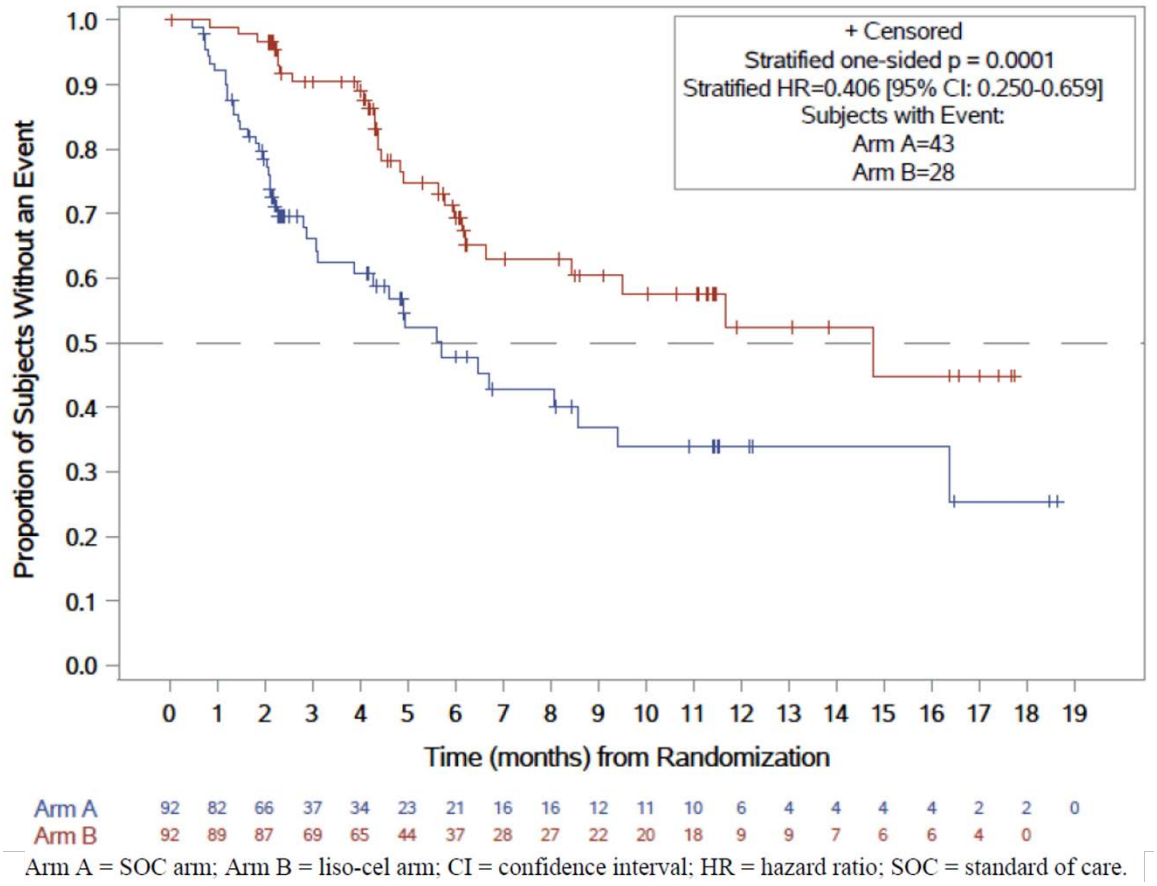
Table 3 shows the results of EFS assessed by the IRC, the primary endpoint, at the secondary interim analysis for efficacy in Study BCM-003 (data cut-off on March 8, 2021). A statistically significant improvement in EFS was observed in the Breyanzi group versus the standard therapy group [see Section 6.1.1.1].

Table 8 and Figure 2 show PFS and its Kaplan-Meier curves, respectively, as of the data cut-off (March 8, 2021).

Table 8. Results of PFS
(Study BCM-003, IRC assessment, efficacy analysis set, data cut-off on March 8, 2021)

	Breyanzi N = 92	Standard therapy N = 92
Number of death or aggravation (%)	28 (30.4)	43 (46.7)
Median [95% CI] (months)	14.8 [6.6, NE]	5.7 [3.9, 9.4]
Hazard ratio [95% CI]*	0.406 [0.250, 0.659]	

* Calculated by stratified Cox proportional hazard model with initial therapeutic effect (PD, SD, PR, or CR with relapse before 3 months, relapse after CR lasting at least 3 months) and sAAIPI (0 or 1 vs. 2 or 3) as the stratification factors.



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; SOC = standard of care.

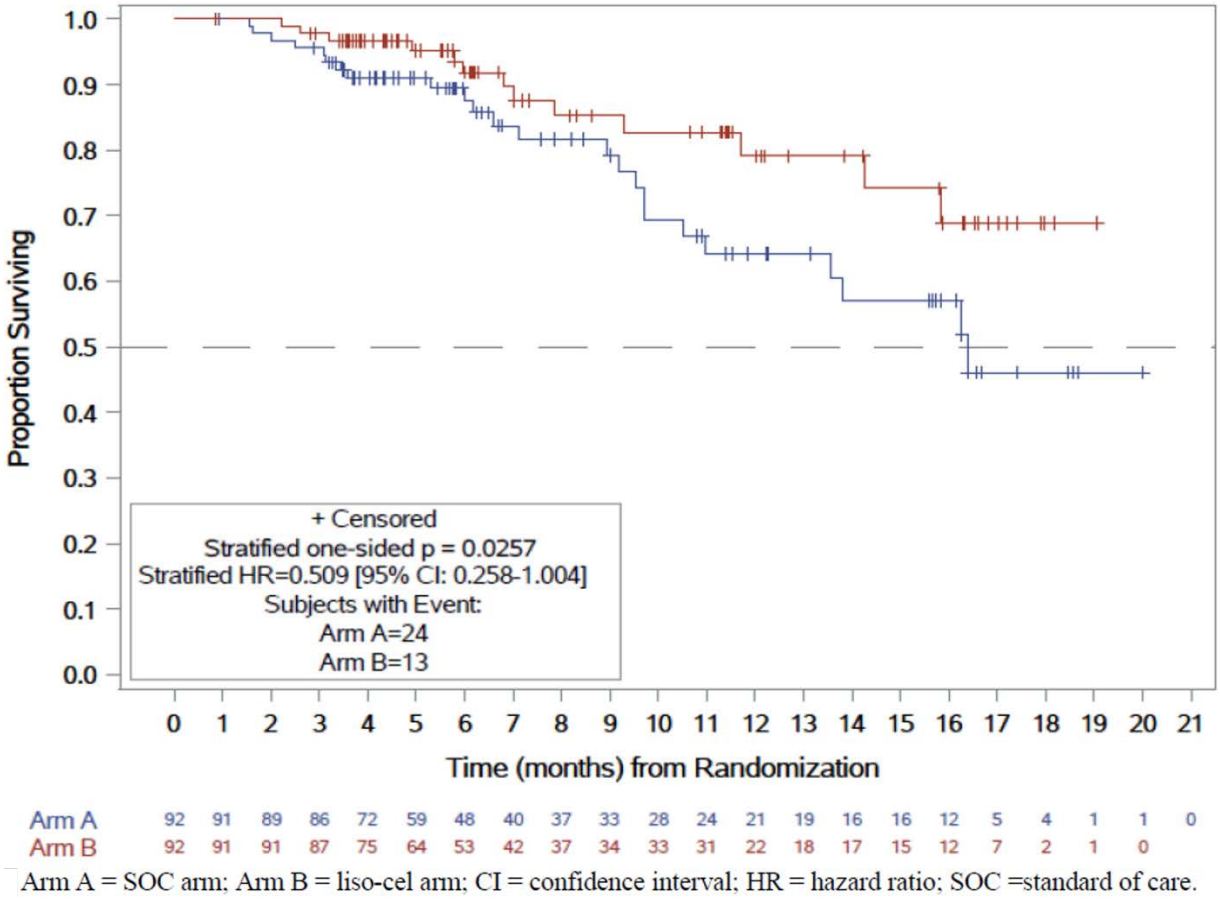
Figure 2. Kaplan-Meier curves of PFS in Study BCM-003
(efficacy analysis set, data cut-off on March 8, 2021)

Table 9 and Figure 3 show OS and its Kaplan-Meier curves, respectively, as of the data cut-off (March 8, 2021).

Table 9. Results of OS (Study BCM-003, efficacy analysis set, data cut-off on March 8, 2021)

	Breyanzi N = 92	Standard therapy N = 92
Number of death (%)	13 (14.1)	24 (26.1)
Median [95% CI] (months)	NE [15.8, NE]	16.4 [11.0, NE]
Hazard ratio [95% CI]*	0.509 [0.258, 1.004]	

* Calculated by stratified Cox proportional hazard model with initial therapeutic effect (PD, SD, PR, or CR with relapse before 3 months, relapse after CR lasting at least 3 month) and sAAIPI (0 or 1 vs. 2 or 3) as the stratification factors.



Arm A = SOC arm; Arm B = liso-cel arm; CI = confidence interval; HR = hazard ratio; SOC =standard of care.

Figure 3. Kaplan-Meier curves of OS in Study BCM-003 (efficacy analysis set, data cut-off on March 8, 2021)

Efficacy evaluation was performed in 46 subjects in the standard therapy group who were allowed to crossover to Breyanzi. Results were as follows: The overall response rate [95% confidence interval (CI)] was 47.8% [32.9%, 63.1%] (CR or PR in 22 subjects, CR in 18 subjects, PR in 4 subjects), and median EFS, PFS, and OS [95% CI] were 3.4 [2.8, 7.8], 3.4 [3.0, 7.8], and 7.8 [6.1, 13.6] months, respectively.

Table 10 shows the efficacy results by histology in Study BCM-003.

Table 10. Efficacy results by histology (IRC assessment)
(Study BCM-003, IRC assessment, efficacy analysis set, data cut-off on March 8, 2021)

	DLBCL NOS				HGBCL	
	de novo		tiNHL			
	Breyanzi n = 53	Standard therapy n = 49	Breyanzi n = 7	Standard therapy n = 8	Breyanzi n = 22	Standard therapy n = 21
EFS events (%)	19 (35.8)	30 (61.2)	2 (28.6)	6 (75.0)	14 (63.6)	19 (90.5)
Median [95% CI] (months)	9.5 [6.1, NE]	3.1 [2.2, 8.1]	NE [1.9, NE]	2.1 [1.2, NE]	4.4 [4.1, 11.7]	2.2 [0.9, 3.9]
Complete response (CR)	37	24	5	3	12	5
Complete response rate (%)	69.8	49.0	71.4	37.5	54.5	23.8
[95% CI*] (%)	[55.7, 81.7]	[34.4, 63.7]	[29.0, 96.3]	[8.5, 75.5]	[32.2, 75.6]	[8.2, 47.2]
Response (CR or PR)	45	27	6	3	18	8
Overall response rate (%)	84.9	55.1	85.7	37.5	81.8	38.1
[95% CI*] (%)	[72.4, 93.3]	[40.2, 69.3]	[42.1, 99.6]	[8.5, 75.5]	[59.7, 94.8]	[18.1, 61.6]
	PMBCL		THRLBCL		FL3B	
	Breyanzi n = 8	Standard therapy n = 10	Breyanzi n = 1	Standard therapy n = 4	Breyanzi n = 1	Standard therapy n = 0
EFS events (%)	0	7 (70.0)	0	1 (25.0)	0	-
Median [95% CI] (months)	NE [NE, NE]	2.2 [1.0, NE]	NE [NE, NE]	NE [2.3, NE]	NE [NE, NE]	-
Complete response (CR)	6	1	0	3	1	
Complete response rate (%)	75.0	10.0	0	75.0	100	-
[95% CI*] (%)	[34.9, 96.8]	[0.3, 44.5]	[0.0, 97.5]	[19.4, 99.4]	[2.5, 100]	
Response (CR or PR)	8	3	1	3	1	
Overall response rate (%)	100	30.0	100	75.0	100	-
[95% CI*] (%)	[63.1, 100]	[6.7, 65.2]	[2.5, 100]	[19.4, 99.4]	[2.5, 100]	

* Clopper-Pearson method

Table 11 shows the efficacy results in the Japanese population of Study BCM-003. In the Japanese population, the hazard ratio of EFS in the Breyanzi group to the standard therapy group was greater than 1, failing to show consistent results with the entire population.

Table 11. Comparison between Japanese population and entire population
(Study BCM-003, IRC assessment, efficacy analysis set, data cut-off on March 8, 2021)

	Japanese population		Entire population	
	Breyanzi n = 5	Standard therapy n = 4	Breyanzi n = 92	Standard therapy n = 92
EFS events (%)	4 (80.0)	2 (50.0)	35 (38.0)	63 (68.5)
Median [95% CI] (months)	4.2 [1.4, NE]	8.6 [2.7, NE]	10.1 [6.1, NE]	2.3 [2.2, 4.3]
Hazard ratio [95% CI]*1	1.104 [0.100, 12.236]		0.349 [0.229, 0.530]	
Best response (number of subjects [%])				
CR	3 (60.0)	3 (75.0)	61 (66.3)	36 (39.1)
PR	1 (20.0)	0	18 (19.6)	8 (8.7)
SD	1 (20.0)	1 (25.0)	4 (4.3)	21 (22.8)
PD	0	0	6 (6.5)	24 (26.1)
Not evaluated	0	0	3 (3.3)	3 (3.3)
Complete response rate [95% CI*2] (%)	60.0 [14.7, 94.7]	75.0 [19.4, 99.4]	66.3 [55.7, 75.8]	39.1 [29.1, 49.9]
Overall response rate [95% CI*2] (%)	80.0 [28.4, 99.5]	75.0 [19.4, 99.4]	85.9 [77.0, 92.3]	47.8 [37.3, 58.3]
Median PFS [95% CI] (months)	4.2 [1.4, NE]	NE [8.6, NE]	14.8 [6.6, NE]	5.7 [3.9, 9.4]
Median OS [95% CI] (months)	NE [6.8, NE]	NE [13.8, NE]	NE [15.8, NE]	16.4 [11.0, NE]

*1 Calculated by stratified Cox proportional hazard model with initial therapeutic effect (PD, SD, PR, or CR relapse before 3 months, CR lasting at least 3 months) and sAAIPI (0 or 1 vs. 2 or 3) as the stratification factors.
*2 Clopper-Pearson method

The following are the possible reasons why the tendencies of results in the Japanese population were different from those in the entire population:

- The number of Japanese subjects evaluated was very limited.
- The Breyanzi group of the Japanese population included a higher proportion of the following subgroups, compared with the entire population: (a) subjects with chemotherapy resistance, a poor

prognostic factor[20] (80.0% [4 of 5 subjects] in the Breyanzi group of the Japanese population, 27.2% [25 of 92 subjects] in the entire population) and (b) subjects with second-line age-adjusted international prognostic index (sAAIPI) score of 2 or 3 (60.0% [3 of 5 subjects] and 39.1% [36 of 92 subjects], respectively).

Based on the above and in view of the following findings, results in the Japanese population are not distinctly different from those in the entire population, despite the limitations to the assessment because of the limited number of Japanese subjects in Study BCM-003:

- When a patient subgroup[21] with similar characteristics to those of the Japanese population was extracted from the non-Japanese population of Study BCM-003, the hazard ratios [95% CI] of EFS, PFS, and OS in the Breyanzi group to those in the standard therapy group were 0.151 [0.052, 0.433], 0.310 [0.097, 0.989], and 0.748 [0.184, 3.032], respectively.
- No difference in the efficacy of Breyanzi was observed between Japanese and non-Japanese patients with relapsed or refractory LBCL or FL3B after 2 lines of prior therapy (the approved indication).
- There is no difference between Japan and foreign countries in the diagnosis or treatment algorithm of relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

PMDA's view:

The above explanation of the applicant is understandable. In light of the following findings, the results of Study BCM-003 demonstrated the efficacy of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are eligible for autologous HSCT:

- A statistically significant improvement in IRC-assessed EFS, the primary endpoint of Study BCM-003, was observed in the Breyanzi group compared to the standard therapy group.
- In Study BCM-003, results of PFS were similar to those observed for EFS.
- In Study BCM-003, there was no tendency of shorter OS in the Breyanzi group than in the standard therapy group.

6.R.2.4 Efficacy in patients ineligible for autologous HSCT

The applicant's explanation about the efficacy of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are ineligible for autologous HSCT:

In Cohort 2 of Study BCM-001 and in Study 017006, the overall response rate was selected as the primary endpoint. This is because response to Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are ineligible for autologous HSCT, the target patient population of the studies, is expected to lead to tumor shrinkage and improved associated symptoms. (*Bone Marrow Transplant.* 2016;51:51-7).

Tables 5 and 7 show the results of the primary endpoint in Cohort 2 of Study BCM-001 and in Study 017006. The overall response rate assessed by IRC [95% CI] was 63.0% [42.4%, 80.6%] and 80.3%

[20] Results of subgroup analyses performed for the Breyanzi group of Study BCM-003 showed that EFS [95% CI] was 5.7 [4.2, 6.1] months in the chemotherapy-resistant subgroup (best response to prior therapy was SD or PD) and not evaluable (NE) [8.4, NE] months in the chemotherapy-responsive subgroup (best response to prior therapy was CR or PR), and 5.8 [4.3, 14.8] months in the subgroup with sAAIPI score of 2 or 3 and NE [6.6, NE] months in the subgroup with sAAIPI score of 0 or 1.

[21] A non-Japanese subgroup consisting of 50 subjects (28 in the Breyanzi group, 22 in the control group) was selected by propensity score matching calculated based on the response to chemotherapy (chemotherapy responsive vs. chemotherapy resistant), sAAIPI in the second-line therapy (0 or 1 vs. 2 or 3), and disease conditions (stage I or II vs. stage III or IV).

[68.2%, 89.4%] for the former and latter studies, respectively [see Sections 6.1.1.2 and 6.1.2.1]. In Cohort 2 of Study BCM-001, no statistically significant difference from the pre-specified threshold (50.2%) was observed, supposedly due to the limited number of subjects and to a higher proportion of patients with poor prognosis (patients with disease stage IV according to the Ann Arbor classification,[22)] patients with sAAIPI score of 2 or 3,[23)] and patients who received bridging chemotherapy for disease control[24)]) than in Study 017006.

In Cohort 2 of Study BCM-001, the complete response rate [95% CI] was 48.1% [28.7%, 68.1%]. In 17 subjects with response, the median duration of response (DOR) [95% CI] was 12.12 [2.23, (not valuable) NE] months and the median EFS, PFS, and OS were 3.29 [1.97, 6.41], 3.55 [1.97, 13.04], and NE [4.27, NE] months, respectively. Among 2 Japanese subjects receiving Breyanzi, response (CR) was observed in 1 subject with DOR of 11.60 months, and EFS in each subject was 12.52 months and 0.66 months (PFS was the same as EFS). Death occurred in 1 subject with PD.

In Study 017006, the complete response rate [95% CI] was 54.1% [40.8%, 66.9%], the median DOR [95% CI] in 49 subjects with response was 12.09 [6.24, NE] months, and the median EFS, PFS, and OS [95% CI] was 7.23 [3.22, 22.60], 9.03 [4.17, NE], and NE [17.28, NE] months, respectively.

Tables 12 and 13 show the efficacy results by histology, demonstrating response in all histological subtypes.

Table 12. Efficacy results by histology
(Cohort 2 of Study BCM-001, IRC assessment, efficacy analysis set, data cut-off on March 2, 2022)

	DLBCL NOS		HGBCL	FL3B	Total
	de novo	tFL			
	n = 18	n = 0	n = 8	n = 1	n = 27
Complete response (CR)	9	-	3	1	13
Complete response rate (%)	50.0	-	37.5	100	48.1
[95% CI*] (%)	[26.0. 74.0]		[8.5, 75.5]	[2.5, 100]	[28.7, 68.1]
Response (CR or PR)	11	-	5	1	17
Overall response rate (%)	61.1	-	62.5	100	63.0
[95% CI*] (%)	[35.7, 82.7]		[24.5, 91.5]	[2.5, 100]	[42.4, 80.6]

* Clopper-Pearson method

Table 13. Efficacy results by histology
(Study 017006, IRC assessment, efficacy analysis set, data cut-off on September 24, 2021)

	DLBCL NOS		HGBCL	FL3B	Total
	de novo	tFL			
	n = 33	n = 9	n = 18	n = 1	n = 61
CR	20	5	7	1	33
Complete response rate (%)	60.6	55.6	38.9	100	54.1
[95% CI*] (%)	[42.1, 77.1]	[21.2, 86.3]	[17.3, 64.3]	[2.5, 100]	[40.8, 66.9]
Response (CR or PR)	28	7	13	1	49
Overall response rate (%)	84.8	77.8	72.2	100	80.3
[95% CI*] (%)	[68.1, 94.9]	[40.0, 97.2]	[46.5, 90.3]	[2.5, 100]	[68.2, 89.4]

* Clopper-Pearson method

22) Cohort 2 of Study BCM-001, 19 of 27 subjects (70.4%); Study 017006, 25 of 61 subjects (41.0%)
23) Cohort 2 of Study BCM-001, 15 of 27 subjects (55.5%); Study 017006, 26 of 61 subjects (42.6%)
24) Cohort 2 of Study BCM-001, 23 of 27 subjects (85.2%); Study 017006, 32 of 61 subjects (52.5%)

According to the reports of the clinical studies in subjects with relapsed or refractory LBCL or FL3B who were ineligible for autologous HSCT (*Haematologica.* 2013;98:1726-31, *Leuk Lymphoma.* 2021;62:2161-8, etc.), the overall response rate ranged from 40% to 50%, the complete response rate ranged from 30% to 40%, the median DOR ranged from 10 to 13 months, the median PFS ranged from 5 to 10 months, and the median OS ranged from 10 to 13 months. In light of the reports, the results of Cohort 2 of Study BCM-001 and Study 017006 suggest the efficacy of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are ineligible for autologous HSCT.

PMDA's view:
The above explanation of the applicant is understandable. The results of Cohort 2 of Study BCM-001 and Study 017006 have demonstrated that Breyanzi has efficacy to a certain extent in the treatment of patients with relapsed or refractory LBCL or FL3B who are ineligible for autologous HSCT.

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

As a result of the following review, PMDA concluded that adverse events requiring special attention during the use of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy are similar to those identified as warranting special attention at the submission for the approved indications,[25)] and that similar caution should be exercised against these adverse events.

PMDA also concluded that Breyanzi is tolerable in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy as well, provided that appropriate measures, such as monitoring and management of adverse events, are taken by a physician with sufficient knowledge and experience in the treatment of LBCL or FL3B at a medical institution well-equipped for responding to these adverse events.

6.R.3.1 Safety profile of Breyanzi

The applicant's explanation about the safety of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy:
Table 14 shows the summary of the safety in Study BCM-003 (data cut-off on March 8, 2021).

[25)] CRS, hemophagocytic lymphohistiocytosis, nerve disorder, infection, bone marrow depression, hypersensitivity, hypogammaglobulinemia, and tumor lysis syndrome (TLS) (Review Report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021)

Table 14. Summary of safety (Study BCM-003, safety analysis set, data cut-off on March 8, 2021)

	n (%)		
	Breyanzi	Standard therapy	Standard therapy, followed by crossover to Breyanzi[*1]
	N = 92	N = 91	N = 47
All adverse events	92 (100)	90 (98.9)	44 (93.6)
Grade ≥3 adverse events	85 (92.4)	79 (86.8)	32 (68.1)
Serious adverse events	44 (47.8)	44 (48.4)	13 (27.7)
Adverse events resulting in death	1 (1.1)	2 (2.2)	0
CRS[*2]	45 (48.9)	-	23 (48.9)
Grade ≥3 CRS	1 (1.1)	-	1 (2.1)
Neurological events[*3]	59 (64.1)	58 (63.7)	26 (55.3)
Grade ≥3 neurological events	12 (13.0)	6 (6.6)	6 (12.8)
CAR T-related neurotoxicity[*4]	11 (12.0)	-	8 (17.0)
Grade ≥3 CAR T-related neurotoxicity	4 (4.3)	-	2 (4.3)
Cytopenia[*5]	84 (91.3)	75 (82.4)	33 (70.2)
Grade ≥3 cytopenia	82 (89.1)	71 (78.0)	29 (61.7)
Infection[*6]	39 (42.4)	36 (39.6)	9 (19.1)
Grade ≥3 infection	14 (15.2)	19 (20.9)	3 (6.4)

*1 Adverse events observed in subjects who were randomized to the standard therapy group and allowed to crossover to Breyanzi
*2 Adverse events coded to "cytokine release syndrome" in the preferred term (PT) of the Medical Dictionary for Regulatory Activities Japanese version (MedDRA)
*3 Adverse events coded to "nervous system disorders" or "psychiatric disorders" in the system organ class (SOC) of MedDRA
*4 Events considered Breyanzi-associated neurotoxicity by the investigator. The investigator received training to prospectively identify all adverse events of potential signs of Breyanzi-associated neurotoxicity and grade the toxicity according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) and to control the neurotoxicity based on its understanding (including the importance of excluding other main causes of neurological symptoms, such as stroke, meningitis, and metabolic encephalopathy).
*5 Events listed in Table 15
*6 Adverse events coded to "infections and infestations" in MedDRA SOC.

Table 15. List of events collected as cytopenia

Classification	MedDRA PT (MedDRA version 23.0)
Erythrocytes decreased	Anaemia, leukoerythroblastic anaemia, anaemia macrocytic, microcytic anaemia, anaemia megaloblastic, normochromic anaemia, haematocrit decreased, normochromic normocytic anaemia, haemoglobin decreased, normocytic anaemia, hyperchromic anaemia, red blood cell count decreased, hypochromic anaemia, sideroblastic anaemia
Neutrocytes decreased	Agranulocytosis, granulocyte count decreased, autoimmune neutropenia, granulocytopenia, band neutrophil count decreased, idiopathic neutropenia, band neutrophil percentage decreased, neutropenia, benign ethnic neutropenia, neutropenic colitis, cyclic neutropenia, neutropenic sepsis, febrile neutropenia, neutropenic infection, Felty's syndrome, neutrophil count decreased
Platelets decreased	Acquired amegakaryocytic thrombocytopenia, platelet production decreased, megakaryocytes decreased, platelet toxicity, platelet count decreased, thrombocytopenia, platelet maturation arrest
Pancytopenia	Aplastic anaemia, febrile bone marrow aplasia, autoimmune aplastic anaemia, full blood count decreased, autoimmune pancytopenia, pancytopenia, bicytopenia, Shwachman-Diamond syndrome, bone marrow failure

In Study BCM-003, adverse events with a ≥10% higher incidence in the Breyanzi group than in the standard therapy group were neutropenia (75 subjects [81.5%] in the Breyanzi group, 49 subjects (53.8%) in the standard therapy group), cytokine release syndrome (45 subjects [48.9%] vs. 0 subjects [0%], respectively), headache (39 subjects [42.4%] vs. 20 subjects [22.0%], respectively), lymphopenia (25 subjects [27.2%] vs. 10 subjects [11.0%], respectively), hypotension (19 subjects [20.7%] vs. 4 subjects [4.4%], respectively), and tremor (11 subjects [12.0%] vs. 0 subjects [0%], respectively).

Grade ≥3 adverse events with a ≥5% higher incidence in the Breyanzi group than in the standard therapy group were neutropenia (74 subjects [80.4%] in the Breyanzi group, 46 subjects [50.5%] in the standard therapy group) and lymphopenia (23 subjects [25.0%] vs. 8 subjects [8.8%], respectively).

The serious adverse event with a ≥5% higher incidence in the Breyanzi group than in the standard therapy group was cytokine release syndrome (12 subjects [13.0%] in the Breyanzi group, 0 subject [0%] in the standard therapy group).

Table 16 shows the summary of safety profile in Study 017006 (data cut-off on September 24, 2021) and Cohort 2 of Study BCM-001 (data cut-off on March 2, 2022).

Table 16. Summary of safety
(Study 017006[*1] and Cohort 2 of Study BCM-001,[*2] safety analysis set)

	n (%)	
	Study 017006 N = 61	Study BCM-001, Cohort 2 N = 27
All adverse events	59 (96.7)	26 (96.3)
Grade ≥3 adverse events	48 (78.7)	25 (92.6)
Serious adverse events	20 (32.8)	8 (29.6)
Adverse events resulting in death	2 (3.3)	1 (3.7)
CRS[*3]	23 (37.7)	13 (48.1)
Grade ≥3 CRS	1 (1.6)	0
Neurological events[*4]	41 (67.2)	9 (33.3)
Grade ≥3 neurological events	5 (8.2)	1 (3.7)
CAR T-related neurotoxicity[*5]	19 (31.1)	4 (14.8)
Grade ≥3 CAR T-related neurotoxicity	3 (4.9)	1 (3.7)
Cytopenia[*6]	45 (73.8)	25 (92.6)
Grade ≥3 cytopenia	39 (63.9)	25 (92.6)
Infection[*7]	11 (18.0)	7 (25.9)
Grade ≥3 infection	4 (6.6)	3 (11.1)

*1 Data cut-off on September 24, 2021
*2 Data cut-off on March 2, 2022
*3 Adverse events coded to “cytokine release syndrome” in MedDRA PT
*4 Adverse events coded to “nervous system disorders” or “psychiatric disorders” in MedDRA SOC
*5 Events considered Breyanzi-associated neurotoxicity by the investigator. The investigator received training to prospectively identify all adverse events of potential signs of Breyanzi-associated neurotoxicity and grade the toxicity according to the NCI-CTCAE and to control the neurotoxicity based on its understanding (including the importance of excluding other main causes of neurological symptoms, such as stroke, meningitis, and metabolic encephalopathy).
*6 Events listed in Table 15
*7 Adverse events coded to “infections and infestations” in MedDRA SOC.

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

Tables 17 and 18 show the summary of the safety in the Japanese population and the non-Japanese population in Study BCM-003 and Cohort 2 of Study BCM-001.

Table 17. Summary of safety in Japanese and non-Japanese populations (Study BCM-003, safety analysis set, data cut-off on March 8, 2021)

	n (%)					
	Breyanzi		Standard therapy		Standard therapy, followed by crossover to Breyanzi[*1]	
	Japanese patients N = 5	Non-Japanese patients N = 87	Japanese patients N = 4	Non-Japanese patients N = 87	Japanese patients N = 2	Non-Japanese patients N = 45
All adverse events	5 (100)	87 (100)	4 (100)	86 (98.9)	2 (100)	42 (93.3)
Grade ≥3 adverse events	5 (100)	80 (92.0)	4 (100)	75 (86.2)	2 (100)	30 (66.7)
Serious adverse events	1 (20.0)	43 (49.4)	0	44 (50.6)	0	13 (28.9)
Adverse events resulting in death	0	1 (1.1)	0	2 (2.3)	0	0
CRS[*2]	4 (80.0)	41 (47.1)	-	-	2 (100)	21 (46.7)
Grade ≥3 CRS	1 (20.0)	0	-	-	0	1 (2.2)
Neurological events[*3]	2 (40.0)	57 (65.5)	1 (25.0)	57 (65.5)	0	26 (57.8)
Grade ≥3 neurological events	0	12 (13.8)	0	6 (6.9)	0	6 (13.3)
CAR T-related neurotoxicity[*4]	0	11 (12.6)	-	-	0	8 (17.8)
Grade ≥3 CAR T-related neurotoxicity	0	4 (4.6)	-	-	0	2 (4.4)
Cytopenia[*5]	5 (100)	79 (90.8)	4 (100)	71 (81.6)	2 (100)	31 (68.9)
Grade ≥3 cytopenia	5 (100)	77 (88.5)	4 (100)	67 (77.0)	2 (100)	27 (60.0)
Infection[*6]	2 (40.0)	37 (42.5)	2 (50.0)	34 (39.1)	0	9 (20.0)
Grade ≥3 infection	1 (20.0)	13 (14.9)	2 (50.0)	17 (19.5)	0	3 (6.7)

*1 Adverse events observed in subjects who randomized to the standard therapy and allowed to crossover to Breyanzi
*2 Adverse events coded to "cytokine release syndrome" in MedDRA PT
*3 Adverse events coded to "nervous system disorders" or "psychiatric disorders" in MedDRA SOC
*4 Events considered Breyanzi-associated neurotoxicity by the investigator. The investigator received training to prospectively identify all adverse events of potential signs of Breyanzi-associated neurotoxicity and grade the toxicity according to the NCI-CTCAE and to control the neurotoxicity based on its understanding (including the importance of excluding other main causes of neurological symptoms, such as stroke, meningitis, and metabolic encephalopathy).
*5 Events listed in Table 15
*6 Adverse events coded to "infections and infestations" in MedDRA SOC.

Table 18. Summary of safety in Japanese and non-Japanese populations (Cohort 2 of Study BCM-001, safety analysis set, data cut-off on March 2, 2022)

	n (%)	
	Japanese patients N = 2	Non-Japanese patients N = 25
All adverse events	2 (100)	24 (96.0)
Grade ≥3 adverse events	2 (100)	23 (92.0)
Serious adverse events	1 (50.0)	7 (28.0)
Adverse events resulting in death	0	1 (4.0)
CRS[*1]	1 (50.0)	12 (48.0)
Grade ≥3 CRS	0	0
Neurological events[*2]	1 (50.0)	8 (32.0)
Grade ≥3 neurological events	0	1 (4.0)
CAR T-related neurotoxicity[*3]	0	4 (16.0)
Grade ≥3 CAR T-related neurotoxicity	0	1 (4.0)
Cytopenia[*4]	2 (100)	23 (92.0)
Grade ≥3 cytopenia	2 (100)	23 (92.0)
Infection[*5]	1 (50.0)	6 (24.0)
Grade ≥3 infection	1 (50.0)	2 (8.0)

*1 Adverse events coded to "cytokine release syndrome" in MedDRA PT
*2 Adverse events coded to "nervous system disorders" or "psychiatric disorders" in MedDRA SOC
*3 Events considered Breyanzi-associated neurotoxicity by the investigator. The investigator received training to prospectively identify all adverse events of potential signs of Breyanzi-associated neurotoxicity and grade the toxicity according to the NCI-CTCAE and to control the neurotoxicity based on its understanding (including the importance of excluding other main causes of neurological symptoms, such as stroke, meningitis, and metabolic encephalopathy).
*4 Events listed in Table 15
*5 Adverse events coded to "infections and infestations" in MedDRA SOC

Table 19 shows all-Grade or Grade ≥3 adverse events with a ≥20% higher incidence in the Japanese population than in the non-Japanese population in the Breyanzi group of Study BCM-003 and Cohort 2 of Study BCM-001.

Table 19. Adverse events with ≥20% higher incidence in Japanese than in non-Japanese patients (Study BCM-003[*1] and Cohort 2 of Study BCM-001,[*2] Safety analysis set)

PT (MedDRA ver.23.0)	n (%)			
	Study BCM-003 Breyanzi	Study BCM-003 Breyanzi	Study BCM-001 Cohort 2	Study BCM-001 Cohort 2
	Japanese patients N = 5	Non-Japanese patients N = 87	Japanese patients N = 2	Non-Japanese patients N = 25
Adverse events with ≥20% higher incidence				
Neutropenia	5 (100)	70 (80.5)	2 (100)	20 (80.0)
Anaemia	4 (80.0)	54 (62.1)	2 (100)	6 (24.0)
Thrombocytopenia	4 (80.0)	49 (56.3)	2 (100)	9 (36.0)
CRS	4 (80.0)	41 (47.1)	1 (50.0)	12 (48.0)
Pyrexia	4 (80.0)	23 (26.4)	1 (50.0)	9 (36.0)
Nausea	4 (80.0)	45 (51.7)	0	3 (12.0)
Hiccups	3 (60.0)	3 (3.4)	0	0
Blood fibrinogen decreased	0	0	2 (100)	0
Hepatic function abnormal	2 (40.0)	0	0	0
Grade ≥3 adverse events with ≥20% higher incidence				
Neutropenia	5 (100)	69 (79.3)	2 (100)	20 (80.0)
Anaemia	4 (80.0)	41 (47.1)	2 (100)	5 (20.0)
Thrombocytopenia	4 (80.0)	41 (47.1)	1 (50.0)	5 (20.0)

*1 Data cut-off on March 8, 2021
*2 Data cut-off on March 2, 2022

There were no adverse events resulting in death in Japanese subjects receiving Breyanzi. Serious adverse events observed were bacterial sepsis in 1 subject in the Breyanzi group of Study BCM-003 and cytomegalovirus infection and septic shock in 1 subject in Cohort 2 of Study BCM-001. The outcome was “resolved” for all of the events.

Despite the limitations to the comparison between the Japanese population and the non-Japanese population because of the limited number of Japanese subjects, there are no new safety concerns about the use of Breyanzi in the Japanese population, suggesting no difference in the profile affecting the safety control.

The applicant’s explanation about the difference in the safety profile of Breyanzi between patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy and patients with the approved indication:

Table 20 shows the summary of safety in the Breyanzi group of Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006 in subjects with relapsed or refractory LBCL or FL3B after 1 line of prior

therapy and Study 017001,[26)] and Cohort 1 and Cohort 3[27)] of Study BCM-001 in subjects with relapsed or refractory LBCL or FL3B after 2 lines of prior therapy, the approved indication. The safety profile of Breyanzi demonstrated in Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006 was similar to that observed for the approved indication.

Table 20. Summary of safety (Breyanzi group of Study BCM-003,[*1] Cohort 2 of Study BCM-001,[*2] Study 017006,[*3] Study 017001 [DLBCL cohort],[*4] Study BCM-001 [Cohorts 1 and 3],[*5] safety analysis set)

	n (%)				
	Study BCM-003 Breyanzi	Study 017006	Study BCM-001 Cohort 2	Study 017001 DLBCL cohort	Study BCM-001 Cohorts 1 and 3
	N = 92	N = 61	N = 27	N = 269	N = 46
All adverse events	92 (100)	59 (96.7)	26 (96.3)	267 (99.3)	46 (100)
Grade ≥3 adverse events	85 (92.4)	48 (78.7)	25 (92.6)	213 (79.2)	43 (93.5)
Serious adverse events	44 (47.8)	20 (32.8)	8 (29.6)	122 (45.4)	20 (43.5)
Adverse events resulting in death	1 (1.1)	2 (3.3)	1 (3.7)	7 (2.6)	3 (6.5)
CRS[*6]	45 (48.9)	23 (37.7)	13 (48.1)	113 (42.0)	19 (41.3)
Grade ≥3 CRS	1 (1.1)	1 (1.6)	0	6 (2.2)	2 (4.3)
Neurological events[*7]	59 (64.1)	41 (67.2)	9 (33.3)	200 (74.3)	23 (50.0)
Grade ≥3 neurological events	12 (13.0)	5 (8.2)	1 (3.7)	40 (14.9)	5 (10.9)
CAR T-related neurotoxicity[*8]	11 (12.0)	19 (31.1)	4 (14.8)	80 (29.7)	9 (19.6)
Grade ≥3 CAR T-related neurotoxicity	4 (4.3)	3 (4.9)	1 (3.7)	27 (10.0)	5 (10.9)
Cytopenia[*9]	84 (91.3)	45 (73.8)	25 (92.6)	206 (76.6)	44 (95.7)
Grade ≥3 cytopenia	82 (89.1)	39 (63.9)	25 (92.6)	194 (72.1)	41 (89.1)
Infection[*10]	39 (42.4)	11 (18.0)	7 (25.9)	110 (40.9)	17 (37.0)
Grade ≥3 infection	14 (15.2)	4 (6.6)	3 (11.1)	33 (12.3)	7 (15.2)

*1 Data cut-off on March 8, 2021
*2 Data cut-off on March 2, 2022
*3 Data cut-off on September 24, 2021
*4 Data cut-off on August 12, 2019
*5 Data cut-off on June 19, 2020
*6 Adverse events coded to "cytokine release syndrome" in MedDRA PT
*7 Adverse events coded to "nervous system disorders" or "psychiatric disorders" in MedDRA SOC
*8 Events considered Breyanzi-associated neurotoxicity by the investigator. The investigator received training to prospectively identify all adverse events of potential signs of Breyanzi-associated neurotoxicity and grade the toxicity according to the NCI-CTCAE and to control the neurotoxicity based on its understanding (including the importance of excluding other main causes of neurological symptoms, such as stroke, meningitis, and metabolic encephalopathy).
*9 Events listed in Table 15
*10 Adverse events coded to "infections and infestations" in MedDRA SOC

PMDA's view:

Caution should be exercised against Grade ≥3 adverse events with a higher incidence in the Breyanzi group than in the standard therapy group and against serious adverse events observed in Study BCM-003. The safety profile observed in the Breyanzi group of Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006 does not clearly differ from the safety profile observed in Cohorts 1 and 3 of Study BCM-001 and Study 017001 in patients with relapsed or refractory LBCL or FL3B, the approved indication. However, serious adverse events such as cytokine release syndrome (CRS) were observed

26) An open-label, uncontrolled study to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory B cell NHL. Breyanzi was infused intravenously (a) as a single dose of target dose of 50×10^6 CAR-positive viable T cells (25×10^6 CD8-positive T cells, 25×10^6 CD4-positive T cells), 100×10^6 CAR-positive viable T cells (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells), or 150×10^6 CAR-positive viable T cells (75×10^6 CD8-positive T cells, 75×10^6 CD4-positive T cells), or (b) at a dose of 50×10^6 CAR-positive viable T cells, followed by the administration of the same dose after 14 days (Review Report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021).

27) An open label, uncontrolled study to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory B cell NHL. Breyanzi was infused intravenously as a single dose of the target dose of 100×10^6 CAR-positive viable T cells (50×10^6 CD8-positive T cells, 50×10^6 CD4-positive T cells) (Review Report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021).

very frequently after Breyanzi infusion. Patients should be monitored very closely after Breyanzi infusion, and adverse events, if any, should be treated by a multidisciplinary approach. As for the difference in the safety between Japanese and non-Japanese patients, adverse events should be more carefully managed in Japanese patients because of a higher incidence of cytopenia in Japanese patients than in non-Japanese patients, although the limited experience with the use of Breyanzi in Japanese patients precludes strict comparison of the safety of Breyanzi between Japanese and non-Japanese patients.

All of the above-mentioned adverse events are known to Breyanzi. The package insert advises that patients should undergo hematology tests periodically. Given these facts, PMDA considers that Breyanzi is tolerable in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy, provided that appropriate measures, such as monitoring and management of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of LBCL and FL3B at a medical institution well-equipped for responding to these adverse events.

6.R.4 Clinical positioning and indications or performance

The proposed "Indications or Performance" of Breyanzi was as follows:

Indications or Performance (Underline and strikethrough denote addition to, and deletion from, respectively, the approved information.)

The following types of 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, T-cell/histiocyte-rich 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~~

The proposed "Precautions Concerning Indications or Performance" section was as follows:

Precautions Concerning Indications or Performance (Strikethrough denotes deletion from the approved information.)

- 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, including the histological subtypes and prior therapy 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 "Indications or Performance" section of the package insert should be specified as shown below and the "Precautions Concerning Indications or Performance" section as proposed.

Indications or Performance (Strikethrough denotes deletion from the proposed text in the partial change application.)

The following types of 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~~, T cell/histiocyte-rich 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.

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

Among the Japanese and foreign clinical practice guidelines, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, B-Cell lymphomas (NCCN Guidelines) recommend Breyanzi for the treatment of patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

Clinical practice guideline

- NCCN Guidelines (v5.2022): Breyanzi infusion is recommended for the treatment of relapsed or refractory LBCL or FL3B ≤12 months after completion of first-line therapy or primary refractory disease (Category 2A[28)]). Breyanzi infusion is also recommended for the treatment of relapsed or refractory LBCL or FL3B after completion of first-line therapy or primary refractory disease in patients ineligible for autologous HSCT (Category 2B[29)]).

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

The Japanese or foreign clinical practice guidelines do not contain the standard therapy for relapsed or refractory LBCL or FL3B in patients ineligible for autologous HSCT, and recommend the use of HDCT in combination with HSCT in patients eligible for autologous HSCT only if the patients have response

[28)] Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
[29)] Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

to a salvage therapy. However, in clinical studies in which patients underwent this recommended therapy, only approximately 30% of the treated patients achieved disease control for an extended period (*J Clin Oncol.* 2010;28:4184-90, *J Clin Oncol.* 2014;32:3490-6, etc.). In addition, more than half of patients who initiated the recommended therapy did not respond to the salvage chemotherapy, failing to complete HDCT in combination with autologous HSCT. New treatment options thus are required for the diseases. Under these circumstances, Breyanzi was shown to be effective and safe in the treatment of patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy in Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006 [see Sections 6.R.2 and 6.R.3]. Breyanzi can be a new treatment option for this patient population.

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) is added to the "Indications or Performance" section of Breyanzi as one of the histological subtypes indicated, based on the following findings: (a) Patients with THRLBCL were included in Study BCM-003, and response (PR) was observed in 1 of 2 subjects[30)] with THRLBCL treated with Breyanzi, and (b) given its mechanism of action, Breyanzi is expected to be effective for the treatment of CD19-positive THRLBCL.

In addition, a discussion is given on the necessity of rules for prior therapy in patients for whom Breyanzi is recommended. Patients with tiNHL or FL3B included in Study BCM-003, Cohort 2 of Study BCM-001, or Study 017006 had to have received 1 line of therapy following a diagnosis of tiNHL or FL3B. In view of this, it is unnecessary to determine prior chemotherapy by histology in the "Indications or Performance" or "Precautions Concerning Indications or Performance" section.

Study BCM-003 did not include patients who experienced a relapse >12 months after achieving CR to 1 line of therapy. PMDA asked the applicant to explain whether Breyanzi infusion is recommended for this patient population.

The applicant's response:
Patients who are refractory to first-line therapy or relapsed within 12 months after CR to first-line therapy have poorer prognosis than patients who experienced a relapse later (*J Clin Oncol.* 2010;28:4184-90). Based on this report, Study BCM-003 was designed to include only patients who were refractory to first-line therapy or relapsed within 12 months after CR to first-line therapy. There is no experience with the use of Breyanzi in patients eligible for autologous HSCT who had a relapse >12 months after CR to first-line therapy. However, the following observations suggest that Breyanzi is recommended as a treatment option for patients eligible for autologous HSCT who had a relapse >12 months after CR to first-line therapy.

- Of patients aged ≤70 years who had a relapse >12 months after CR to first-line therapy, only 57% completed HDCT in combination with autologous HSCT. In addition, the shorter the time to relapse, the poorer the prognosis even among patients who remained relapse-free for >12 months after CR to first-line therapy (*Br J Haematol.* 2022;198:267-77).
- In Cohort 2 of study BCM-001 and Study 017006 in patients with relapsed or refractory LBCL or FL3B who are ineligible for HSCT, the overall response rate [95% CI] and the complete response

30) Patients with THRLBCL receiving Breyanzi in Study BCM-003 were 1 subject in the Breyanzi group and 1 subject in the standard therapy group who was allowed to crossover to Breyanzi.

rate [95% CI] in patients who received Breyanzi after relapse that occurred >12 months after CR to first-line therapy were both 57.1% [18.4%, 90.1%] in 7 subjects in Cohort 2 of Study BCM-001 and 100% [78.2%, 100%] and 80.0% [51.9%, 95.7%], respectively, in 17 subjects of Study 017006, showing that the efficacy in both studies was similar to that in the entire population.[31)]

PMDA's view:
It is generally acceptable to determine "Indications or Performance" based on the results of Study BCM-003, Cohort 2 of Study BCM-001, and Study 017006. However, since THRLBCL is one of the histological subtypes including DLBCL, THRLBCL should be described in the "Clinical Studies" section of the package insert as one of the histological subtypes including DLBCL investigated in clinical studies, instead of adding to "Indications or Performance." Although the applicant's explanation about rules for prior therapy is understandable, there are no clinical study data that investigated the efficacy of Breyanzi versus the conventional therapy in patients eligible for autologous HSCT who had a relapse >12 months after CR to first-line therapy, with the clinical positioning of Breyanzi remaining unclear in this patient population. Therefore, the fact that Study BCM-003 was conducted in patients who had a relapse within 12 months after CR to first-line therapy is important information for deciding whether to use Breyanzi in patients who had a relapse after first-line therapy. Based on the above, the "Clinical Studies" section of the package insert should not only describe the histological subtype and prior therapy of patients enrolled in each study but also specify that Study BCM-003 included patients who had a relapse within 12 months after CR to first-line therapy. Further, the "Precautions Concerning Indications or Performance" section should specify 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.

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

The proposed "Dosage and Administration or Method of Use" for Breyanzi in the present application is the same as approved.

The applicant's explanation about the rationale for the proposed "Dosage and Administration or Method of Use" for Breyanzi.
In Study BCM-003, Study 017006, and Cohort 2 of Study BCM-001, Breyanzi was administered according to the approved "Dosage and Administration or Method of Use." The studies demonstrated the efficacy and safety of Breyanzi. Accordingly, the same "Dosage and Administration or Method of Use" as that for the approved indication was selected also for treatment of patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

PMDA's view:
The applicant's explanation is understandable. The same "Dosage and Administration or Method of Use" as that for the approved indication can be selected also for treatment of patients with relapsed or

[31)] In Cohort 2 of Study BCM-001, the overall response rate [95% CI] and the complete response rate [95% CI] in the entire population were 63.0% [42.4%, 80.6%] and 48.1% [28.7%, 68.1%], respectively (Table 5). In Study 017006, the overall response rate [95% CI] and the complete response rate [95% CI] in the entire population were 80.3% [68.2%, 89.4%] and 54.1% [40.8%, 66.9%], respectively (Table 7).

refractory LBCL or FL3B after 1 line of prior therapy, taking account of the reviews in Sections "6.R.2 Efficacy" and "6.R.3 Safety."

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

The applicant's explanation:

In Study BCM-003, Study 017006, and Cohort 2 of Study BCM-001, the safety profile of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy was shown to be the same as that in the approved indication [see Section 6.R.3.1]. For this and other reasons, patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy will be included in the ongoing post-marketing database surveillance[32)] on all patients receiving Breyanzi for the approved indication.

PMDA's view:

There is only extremely limited experience with the use of Breyanzi in Japanese patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy. The applicant should conduct the post-marketing database surveillance as planned by the applicant to collect safety information and provide the information thus obtained promptly to healthcare professionals.

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." The most common adverse events other than death are shown below.

8.1 Global phase III study (Study BCM-003)

Adverse events were observed in all subjects in the Breyanzi group and in 90 of 91 subjects (98.9%) in the standard therapy group. Adverse events for which a causal relationship to the study therapy could not be ruled out were observed in 88 of 92 subjects (95.7%) in the Breyanzi group and in 84 of 91 subjects (92.3%) in the standard therapy group (42 of 47 subjects [89.4%] after crossover to Breyanzi). Adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 78 of 92 subjects (84.8%) in the Breyanzi group and in 39 of 47 subjects (83%) in the standard therapy + crossover to Breyanzi group. Table 21 shows adverse events occurring in ≥10% of subjects in any group.

32) Safety specifications
CRS, nervous system events, infection, hypogammaglobulinemia, macrophage activation syndrome (hemophagocytic lymphohistiocytosis), TLS, hematocytopenia (including bone marrow failure), hypersensitivity, autoimmune disorder, aggravation of graft versus host disease, secondary carcinogenesis (including carcinogenesis due to insertional mutagenesis caused by lentiviral vector), brain edema, effect on pregnancy and breast-feeding, and long-term safety

Table 21. Adverse events occurring in ≥10% of subjects in any group (Study BCM-003)

SOC PT (MedDRA ver.23.0)	n (%)					
	Breyanzi N = 92		Standard therapy N = 91		Standard therapy, followed by crossover to Breyanzi* N = 47	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	92 (100)	85 (92.4)	90 (98.9)	79 (86.8)	44 (93.6)	32 (68.1)
Blood and lymphatic system disorders						
Neutropenia	75 (81.5)	74 (80.4)	49 (53.8)	46 (50.5)	20 (42.6)	18 (38.3)
Anaemia	58 (63.0)	45 (48.9)	58 (63.7)	45 (49.5)	18 (38.3)	13 (27.7)
Thrombocytopenia	53 (57.6)	45 (48.9)	62 (68.1)	58 (63.7)	16 (34.0)	14 (29.8)
Febrile neutropenia	14 (15.2)	11 (12.0)	22 (24.2)	19 (20.9)	4 (8.5)	4 (8.5)
Lymphopenia	25 (27.2)	23 (25.0)	10 (11.0)	8 (8.8)	5 (10.6)	5 (10.6)
Leukopenia	14 (15.2)	14 (15.2)	13 (14.3)	11 (12.1)	5 (10.6)	5 (10.6)
Gastrointestinal disorders						
Nausea	49 (53.3)	3 (3.3)	52 (57.1)	3 (3.3)	10 (21.3)	1 (2.1)
Diarrhoea	23 (25.0)	0	38 (41.8)	3 (3.3)	6 (12.8)	0
Constipation	31 (33.7)	2 (2.2)	22 (24.2)	0	9 (19.1)	0
Vomiting	18 (19.6)	1 (1.1)	23 (25.3)	2 (2.2)	6 (12.8)	0
Abdominal pain	13 (14.1)	3 (3.3)	12 (13.2)	1 (1.1)	4 (8.5)	1 (2.1)
Dyspepsia	5 (5.4)	0	10 (11.0)	0	1 (2.1)	0
Stomatitis	5 (5.4)	0	10 (11.0)	2 (2.2)	0	0
General disorders and administration site conditions						
Fatigue	36 (39.1)	0	35 (38.5)	2 (2.2)	7 (14.9)	0
Pyrexia	27 (29.3)	0	21 (23.1)	0	6 (12.8)	0
Oedema peripheral	15 (16.3)	1 (1.1)	16 (17.6)	0	5 (10.6)	0
Asthenia	10 (10.9)	1 (1.1)	8 (8.8)	0	3 (6.4)	0
Mucosal inflammation	4 (4.3)	0	12 (13.2)	3 (3.3)	0	0
Metabolism and nutrition disorders						
Decreased appetite	21 (22.8)	1 (1.1)	28 (30.8)	3 (3.3)	7 (14.9)	0
Hypokalaemia	19 (20.7)	4 (4.3)	20 (22.0)	4 (4.4)	7 (14.9)	0
Hypomagnesaemia	13 (14.1)	0	19 (20.9)	1 (1.1)	4 (8.5)	0
Hypophosphataemia	6 (6.5)	3 (3.3)	12 (13.2)	6 (6.6)	3 (6.4)	2 (4.3)
Hypocalcaemia	7 (7.6)	0	5 (5.5)	0	5 (10.6)	0
Nervous system disorders						
Headache	39 (42.4)	4 (4.3)	20 (22.0)	1 (1.1)	10 (21.3)	0
Dizziness	20 (21.7)	0	13 (14.3)	0	5 (10.6)	0
Peripheral sensory neuropathy	7 (7.6)	0	11 (12.1)	0	2 (4.3)	0
Tremor	11 (12.0)	1 (1.1)	0	0	7 (14.9)	0
Musculoskeletal and connective tissue disorders						
Back pain	15 (16.3)	1 (1.1)	16 (17.6)	2 (2.2)	4 (8.5)	2 (4.3)
Arthralgia	13 (14.1)	0	9 (9.9)	0	2 (4.3)	0
Bone pain	12 (13.0)	0	9 (9.9)	0	2 (4.3)	0
Myalgia	11 (12.0)	1 (1.1)	4 (4.4)	0	3 (6.4)	1 (2.1)
Respiratory, thoracic and mediastinal disorders						
Cough	13 (14.1)	0	8 (8.8)	0	2 (4.3)	0
Dyspnoea	13 (14.1)	1 (1.1)	8 (8.8)	1 (1.1)	2 (4.3)	0
Immune system disorders						
CRS	45 (48.9)	1 (1.1)	0	0	23 (48.9)	1 (2.1)
Vascular disorders						
Hypotension	19 (20.7)	3 (3.3)	4 (4.4)	0	5 (10.6)	1 (2.1)
Hypertension	10 (10.9)	4 (4.3)	7 (7.7)	1 (1.1)	5 (10.6)	2 (4.3)
Psychiatric disorders						
Insomnia	19 (20.7)	0	11 (12.1)	0	4 (8.5)	0
Confusional state	5 (5.4)	1 (1.1)	2 (2.2)	2 (2.2)	5 (10.6)	2 (4.3)
Cardiac disorders						
Tachycardia	9 (9.8)	0	10 (11.0)	0	1 (2.1)	0

* Adverse events observed in subjects who were randomized to the standard therapy group and subsequently allowed to crossover to Breyanzi

Serious adverse events were observed in 44 of 92 subjects (47.8%) in the Breyanzi group and in 44 of 91 subjects (48.4%) in the standard therapy group. In the Breyanzi group, serious adverse events observed in ≥2 subjects were CRS in 12 subjects, febrile neutropenia and neutropenia in 7 subjects each, pyrexia in 6 subjects, thrombocytopenia in 4 subjects, anaemia, COVID-19, sepsis, peripheral swelling, aphasia, headache, and pulmonary embolism in 2 subjects each. A causal relationship to Breyanzi could not be ruled out for CRS in 12 subjects, neutropenia in 5 subjects, thrombocytopenia and pyrexia in 3 subjects each, anaemia, febrile neutropenia, and aphasia in 2 subjects each, and sepsis in 1 subject.

In the standard therapy group, serious adverse events observed in ≥2 subjects were febrile neutropenia in 9 subjects, pyrexia in 7 subjects, acute kidney injury in 5 subjects, neutropenia in 4 subjects, anaemia, Escherichia sepsis, pneumonia, and confusional state in 2 subjects each. A causal relationship to the standard therapy could not be ruled out for febrile neutropenia in 9 subjects, pyrexia in 6 subjects, neutropenia in 4 subjects, acute kidney injury in 3subjects, Escherichia sepsis and confusional state in 2 subjects each, anaemia, and pneumonia in 1 subject each.

According to safety data from the subjects who were randomized to the standard therapy group and subsequently allowed to crossover to Breyanzi, serious adverse events observed in ≥2 subjects were CRS in 4 subjects, febrile neutropenia in 3 subjects, and encephalopathy in 2 subjects. A causal relationship to Breyanzi could not be ruled out for CRS in 4 subjects, febrile neutropenia in 3 subjects, and encephalopathy in 2 subjects.

8.2 Global phase II study (Cohort 2 of Study BCM-001)

Adverse events were observed in 26 of 27 subjects (96.3%) in the Breyanzi group, and adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 24 of 27 subjects (88.9%). Table 22 shows all-Grade adverse events with an incidence of ≥10%.

Table 22. Adverse events with an incidence of ≥10% (Cohort 2 of Study BCM-001)

SOC PT (MedDRA ver.23.0)	n (%) N = 27 All Grades	 Grade ≥3
All adverse events	26 (96.3)	25 (92.6)
Blood and lymphatic system disorders		
Neutropenia	22 (81.5)	22 (81.5)
Thrombocytopenia	11 (40.7)	6 (22.2)
Anaemia	8 (29.6)	7 (25.9)
Leukopenia	5 (18.5)	4 (14.8)
Lymphopenia	4 (14.8)	3 (11.1)
General disorders and administration site conditions		
Pyrexia	10 (37.0)	0
Oedema peripheral	5 (18.5)	0
Gastrointestinal disorders		
Constipation	3 (11.1)	1 (3.7)
Diarrhoea	3 (11.1)	0
Nausea	3 (11.1)	0
Immune system disorders		
CRS	13 (48.1)	0
Nervous system disorders		
Headache	4 (14.8)	0
Metabolism and nutrition disorders		
Hypokalaemia	3 (11.1)	1 (3.7)
Hypophosphataemia	3 (11.1)	0
Infections and infestations		
Escherichia urinary tract infection	3 (11.1)	1 (3.7)
Vascular disorders		
Hypertension	3 (11.1)	1 (3.7)

Serious adverse events were observed in 8 of 27 subjects (29.6%). Serious adverse events observed were ascites, constipation, gastric haemorrhage, CRS, hemophagocytic lymphohistiocytosis, conjunctivitis, cytomegalovirus infection, septic shock, amnesia, aphasia, dysarthria, lethargy, somnolence, tremor, thrombocytopenia, cardiac failure, ulcerative keratitis, muscular weakness, squamous cell carcinoma of head and neck, and confusional state in 1 subject each. A causal relationship to Breyanzi could not be ruled out for CRS, hemophagocytic lymphohistiocytosis, amnesia, aphasia, dysarthria, lethargy, somnolence, tremor, thrombocytopenia, ulcerative keratitis, conjunctivitis, muscular weakness, and confusional state in 1 subject each.

8.3 Foreign phase II study (Study 017006)

Adverse events were observed in 59 of 61 subjects (96.7%) in the Breyanzi group, and adverse events for which a causal relationship to Breyanzi could not be ruled out were observed in 48 of 61 subjects (78.7%). Table 23 shows all-Grade adverse events with an incidence of ≥10%.

Table 23. Adverse events with an incidence of ≥10% (Study 017006)

SOC PT (MedDRA ver.23.0)	n (%) N = 61 All Grades	 Grade ≥3
All adverse events	59 (96.7)	48 (78.7)
Blood and lymphatic system disorders		
Neutropenia	31 (50.8)	29 (47.5)
Anaemia	19 (31.1)	7 (11.5)
Thrombocytopenia	17 (27.9)	12 (19.7)
Leukopenia	14 (23.0)	13 (21.3)
Lymphopenia	8 (13.1)	8 (13.1)
General disorders and administration site conditions		
Fatigue	24 (39.3)	0
Oedema peripheral	9 (14.8)	0
Nervous system disorders		
Tremor	10 (16.4)	0
Dizziness	8 (13.1)	0
Headache	7 (11.5)	1 (1.6)
Gastrointestinal disorders		
Nausea	15 (24.6)	1 (1.6)
Diarrhoea	10 (16.4)	0
Constipation	8 (13.1)	0
Immune system disorders		
CRS	23 (37.7)	1 (1.6)
Metabolism and nutrition disorders		
Hypokalaemia	11 (18.0)	2 (3.3)
Hypomagnesaemia	11 (18.0)	1 (1.6)
Decreased appetite	8 (13.1)	1 (1.6)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (13.1)	0
Dyspnoea	7 (11.5)	1 (1.6)
Psychiatric disorders		
Confusional state	9 (14.8)	2 (3.3)
Insomnia	8 (13.1)	0
Vascular disorders		
Hypotension	11 (18.0)	1 (1.6)

Serious adverse events were observed in 20 of 61 subjects (32.8%). Serious adverse events observed were CRS in 8 subjects, confusional state in 3 subjects, upper gastrointestinal haemorrhage, muscular weakness, and pulmonary embolism in 2 subjects each, lower gastrointestinal haemorrhage, obstruction gastric, bacteraemia, COVID-19, COVID-19 pneumonia, Staphylococcal infection, Stenotrophomonas sepsis, arthralgia, neck pain, disorientation, fall, hip fracture, blood bilirubin increased, weight decreased, febrile neutropenia, decreased appetite, headache, and hypotension in 1 subject each. A causal relationship to Breyanzi could not be ruled out for CRS in 8 subjects, confusional state in 3 subjects, disorientation, febrile neutropenia, COVID-19, and muscular weakness in 1 subject 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 inspection and assessment are currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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 LBCL or FL3B after 1 line of prior therapy, and that Breyanzi has acceptable safety in view of its benefits. It is therefore of significance to make Breyanzi available in clinical practice because it offers a new treatment option for patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

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

Review Report (2)

November 21, 2022

Product Submitted for Approval

Brand Name	Breyanzi Suspension for Intravenous Infusion
Non-proprietary Name	Lisocabtagene maraleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	March 25, 2022

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 IRC-assessed EFS, the primary efficacy endpoint, of Study BCM-003 conducted in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy who are eligible for autologous HSCT was statistically significantly longer in the Breyanzi group than in the standard therapy group. PMDA, therefore, concluded that the efficacy of Breyanzi has been demonstrated in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

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 during the use of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy are the same as those[33)] identified in the review of the initial application, and that caution should be exercised against these adverse events as in the use of Breyanzi for the approved indication.

33) CRS, hemophagocytic lymphohistiocytosis, nerve disorder, infection, bone marrow depression, hypersensitivity, hypogammaglobulinemia, and TLS (Review Report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021)

PMDA also concluded that Breyanzi is tolerable, provided that appropriate measures, such as monitoring and management of adverse events, are taken by a physician with sufficient knowledge and experience in the treatment of LBCL or FL3B at a medical institution well-equipped for responding to these adverse events.

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

1.3 Clinical positioning and indications or performance

As a result of the review in Section "6.R.4 Clinical positioning and indications or performance" of Review Report (1), PMDA concluded that the "Clinical Studies" section of the package insert should include the histological subtypes and prior therapy of patients enrolled in clinical studies and should specify that Study BCM-003 included patients who had a relapse within 12 months after CR to first-line therapy, and that the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections should be described as per the relevant sections of the Review Report (1).

Indications or Performance

The following types of 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.

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.
- 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, including the histological subtypes and prior therapy of patients enrolled in the clinical studies.

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

PMDA requested the applicant to modify the "Indications 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 it is acceptable to specify the "Dosage and Administration or Method of Use" as approved with the initial application.

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

1.5 Post-marketing surveillance plan (draft)

The applicant proposed a post-marketing surveillance plan (draft) shown in Table 24 at the time of submission of the present application because the safety profile of Breyanzi in patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy is similar to that for the approved indication. The applicant plans to expand the target patients for the post-marketing database surveillance planned at the initial approval of Breyanzi to all patients treated with Breyanzi, including patients with relapsed or refractory LBCL or FL3B after 1 line of prior therapy.

PMDA's view:

Data on the safety and efficacy of Breyanzi in patients with relapsed or refractory LBCL or FL3B can be collected by setting the target number of patients for the surveillance at 300, including both patients with the approved indication and patients with the proposed indication in the present application. Based on the review in Section "7. Risk Analysis and Outline of the Review Conducted by PMDA" in Review Report (1), the proposed post-marketing surveillance plan is acceptable.

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

Table 24. Outline of post-marketing surveillance plan

Objective	To evaluate the safety and efficacy of Breyanzi in clinical use
Survey method	All-case surveillance The applicant will obtain data on 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 LBCL or FL
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 Efficacy: Best response, PFS, OS

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

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

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

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

The new regenerative medical product application data (CTD 5.3.5.1.1) 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.

3. 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. The re-examination period for the present application is the remainder of the re-examination period for the initial approval (until March 21, 2031).

Indications or Performance

The following types of 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~~, T cell/histiocyte-rich 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.

(Strikethrough denotes deletions.)

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.

(No change)

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

AUC	Area under the curve
Breyanzi	Breyanzi Suspension for Intravenous Infusion
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus disease
CR	complete response
CRS	cytokine release syndrome
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
DLBCL NOS	diffuse large B-cell lymphoma, Not otherwise specified
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FL3B	follicular lymphoma grade 3B
Fludarabine	Fludarabine Phosphate
HDCT	high dose chemotherapy
HGBCL	high grade B-cell lymphoma
HSCT	hematopoietic stem cell transplant
ICU	intensive care unit
IPI	international prognostic index
IRC	Independent Response Committee
LBCL	large B-cell lymphoma
LD chemotherapy	lymphodepleting chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	not evaluable
NHL	non-Hodgkin lymphoma
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PMBCL	primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PR	partial response
PS	performance status
PT	preferred term
sAAIPI	second-line age-adjusted IPI
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	stable disease
SOC	system organ class
Study BCM-001	Study JCAR017- BCM-001
Study BCM-003	Study JCAR017- BCM-003
Submission of application	Submission of application for marketing approval
tFL	transformed follicular lymphoma
THRLBCL	T-cell/histiocyte-rich large B-cell lymphoma

tiNHL	transformed indolent non-Hodgkin lymphoma
TLS	tumor lysis syndrome
Tocilizumab	Tocilizumab (Genetical Recombination)
WHO	World Health Organization