July 19, 2024
Medical Device Evaluation Division
Pharmaceutical Safety 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	November 20, 2023 (Application for partial change approval)

Results of Deliberation

In the meeting held on July 19, 2024, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

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

Review Report

July 3, 2024
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
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Applicant	Bristol-Myers Squibb K.K.
Date of Application	November 20, 2023

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 a new indication

Items Warranting Special Mention
Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 25 of 2023 [*R5 sai*]; PSEHB/MDED Notification No. 0320-1 dated March 23, 2023, 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 follicular lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications or Performance

The following 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.

Dosage and Administration or Method of Use

Leukapheresis at the medical institution and transportation to the manufacturing site

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

Receipt of Breyanzi at the medical institution and administration

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

Approval Conditions

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

Attachment

Review Report (1)

May 22, 2024

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
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Non-proprietary Name	Lisocabtagene maraleucel
Applicant	Bristol-Myers Squibb K.K.
Date of Application	November 20, 2023

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

Relapsed or refractory follicular lymphoma <u>(Grade 1, 2, 3A, or 3B)</u>

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen.

(Underline denotes additions.)

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)

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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[1)])" 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 or more lines of prior therapy (i.e., for use in the third-line plus setting). Breyanzi was also approved in December 2022 for the treatment of relapsed or refractory LBCL and FL3B after 1 line of prior therapy (i.e., for use in the second-line setting).

Breyanzi was designated as an orphan regenerative medical product with the intended indications or performance of the treatment of "follicular lymphoma (Grade 1, 2, or 3A) and marginal zone lymphoma" on March 23, 2023 (Orphan Regenerative Medical Product Designation No. 25 of 2023 [*R5 sai*]).

1.2 Development history etc.

For the clinical development of Breyanzi for the treatment of relapsed or refractory follicular lymphoma (FL), the applicant initiated a global phase II study (Study JCAR017-FOL-001 [Study FOL-001], Cohorts 1 to 3) involving patients with relapsed or refractory FL (Grade 1, 2, or 3A) in July 2020.

In the US, an application for marketing approval of Breyanzi was submitted in November 2023 based on the results from Study FOL-001 as the pivotal data. In May 2024, Breyanzi was approved for the following indication or performance.

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

BREYANZI is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy.

In Japan, the applicant started patient enrollment in Study FOL-001 in [redacted] 20[redacted].

A partial change application has been submitted to add the treatment of relapsed or refractory FL (Grade 1, 2, or 3A) to the indications or performance of Breyanzi, based on the results from Study FOL-001 (Cohorts 1 to 3).

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

The 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 the data on the biological disposition of Breyanzi obtained in Study FOL-001. The results were confirmed to be similar to those submitted for the approval of the initial application and for the approval of partial change application in December 2022.

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

The applicant submitted efficacy and safety evaluation data from 1 global phase II study shown in Table 1.

Table 1. List of clinical study on efficacy and safety

Data category	Region	Study identifier	Phase	Population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Global	FOL-001 (Cohorts 1-3)	II	Patients with relapsed or refractory FL (Grade 1, 2, or 3A)	139	A single intravenous infusion of 100×10^6 anti-CD19 CAR T cells	Efficacy Safety

The clinical study is summarized in the following subsection. The most common adverse events other than deaths reported in the clinical study are presented in Section “8. Adverse Events Observed in Clinical Studies.”

6.1 Evaluation data

6.1.1 Global study

6.1.1.1 Global phase II study (CTD 5.3.5.2-1; Cohorts 1 to 3 of Study FOL-001, ongoing since July 2020 [data cut-off on January 27, 2023])

An open label, uncontrolled study (Study FOL-001) was conducted at 30 study sites (including 4 Japanese study sites) in 10 countries to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory FL (Grade 1, 2, or 3A) (target sample size, 110 patients[2)] [50 in Cohort 1, 40 in Cohort 2, and 20 in Cohort 3]). Table 2 shows the key inclusion/exclusion criteria. The efficacy and safety of Breyanzi were evaluated in the following subject groups: Cohort 1 comprising patients with relapsed or refractory FL who have received 3 or more lines of prior therapy (i.e., in the fourth-line plus setting), Cohort 2 comprising patients with relapsed or refractory FL who have received 2 lines of prior therapy (i.e., in third-line setting), and Cohort 3 comprising patients with high-risk relapsed or refractory FL who have received 1 line of prior therapy (i.e., in the second-line setting).

Table 2. Key inclusion/exclusion criteria

Inclusion criteria
- Patients aged ≥18 years with relapsed or refractory FL (Grade 1, 2, or 3A)
- Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1

Cohort 1 (fourth-line and subsequent treatment):
- Patients who have received ≥3 lines of prior systemic therapy, including ≥1 line of combination therapy with an anti-CD20 antibody-targeted agent (rituximab, obinutuzumab, etc.) and an alkylating agent. HSCT is allowed as a pre-treatment regimen.

Cohort 2 (third-line treatment)
- Patients who have received 2 lines of prior systemic therapy, including ≥1 line of combination therapy with an anti-CD20 antibody-targeted agent (rituximab, obinutuzumab, etc.) and an alkylating agent. HSCT is allowed as a pre-treatment regimen.

Cohort 3 (second-line treatment)
- Patients who have received 1 line of prior combination systemic therapy with an anti-CD20 antibody-targeted agent (rituximab, obinutuzumab, etc.) and an alkylating agent
- Patients with POD24 (defined as subjects who showed progression of disease within 24 months after diagnosis and received treatment within 6 months after the initial diagnosis of FL) OR patients who meet ≥1 of the modified GELF criteria ([a] to [d] below, NCCN Guidelines [v4.2019]):
  (a) Symptoms caused by FL (irrespective of systemic or B symptoms)
  (b) Imminent organ dysfunction, cytopenia secondary to lymphoma, bulky disease (any tumor mass with a diameter >7 cm or at least 3 nodal sites, each with a diameter >3 cm)
  (c) Splenomegaly
  (d) Progression lasting for ≥6 months

Exclusion criteria
- Patients with composite lymphoma consisting of DLBCL and FL, or with evidence or history of histological transformation
- Patients with prior CAR T cell or other genetically-modified cell therapies
- Patients with malignancy involving the CNS only (patients with secondary CNS lesions are eligible for enrollment.)

Study FOL-001 consisted of a pre-treatment period (after screening and from leukapheresis through Breyanzi manufacturing to the start of lymphodepleting chemotherapy [LD chemotherapy]), treatment period (from the start of LD chemotherapy to Day 29 after Breyanzi infusion), and post-treatment follow-up period (from Day 30 after Breyanzi infusion to Year 5 after Breyanzi infusion).

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2) In Cohort 1, assuming an expected overall response rate of 74% based on the Independent Response Committee (IRC) assessment for the primary endpoint, the number of subjects necessary to ensure 90% statistical power (the target number of enrolled patients) was determined to be 50 at the threshold of 50% and one-sided significance level of 2.5%.
In Cohort 2, assuming an expected rate of 77% for the primary endpoint in the combined population of Cohorts 1 and 2, the number of subjects necessary to ensure 90% statistical power was determined to be 90 at the threshold of 60% and one-sided significance level of 2.5%, and thus the target number of enrolled patients was determined to be 40.
In Cohort 3, assuming an expected rate of 80% for the primary endpoint, the number of subjects necessary to ensure 80% statistical power (the target number of enrolled patients) was determined to be 20 at the threshold of 50% and one-sided significance level of 2.5%.

Breyanzi was intravenously infused as a single dose of 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells and 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 hydrate (cyclophosphamide) 300 mg/m^2 once daily 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. The bridging chemotherapy had to be completed ≥7 days before the start of LD chemotherapy.

A total of 139 patients (65 in Cohort 1, 49 in Cohort 2, and 25 in Cohort 3) underwent leukapheresis and were enrolled. Of these, 137 patients received LD chemotherapy and the remaining 2 patients discontinued the clinical study (1 in Cohort 1 [meeting the exclusion criteria] and 1 in Cohort 3 [failure to meet the inclusion criteria]). Of the 137 patients, 130 subjects received Breyanzi (59 in Cohort 1, 48 in Cohort 2, and 23 in Cohort 3). The remaining 7 subjects were excluded (5 in Cohort 1 [administration of out-of-specification (OOS) product in 3[3)], death caused by adverse event in 1, and unknown reason[4)] in 1], 1 in Cohort 2 [administration of OOS product[5)]], and 1 in Cohort 3 [administration of OOS product[6)]]). All subjects who received Breyanzi were included in the safety analysis set. Of the 130 subjects receiving Breyanzi, 124 subjects were included in the efficacy analysis set, and the remaining 6 subjects in Cohort 1 were excluded (3 with missing Independent Response Committee [IRC]-assessed baseline positron emission tomography [PET] scans, 2 with missing post-bridging therapy PET scans, and 1 who had no PET-positive disease at baseline per IRC assessment). Ten Japanese subjects (6 in Cohort 1, 3 in Cohort 2, and 1 in Cohort 3) were enrolled in the study and all of them received Breyanzi.

The primary efficacy endpoint of Study FOL-001 was defined as the IRC-assessed overall response rate based on the Lugano criteria (*J Clin Oncol*. 2014,32:3059-68).

The primary analysis was performed after the target number of subjects were followed up for approximately 12 months after the initial response (complete response [CR] or partial response [PR]) or until death, disease progression, or study discontinuation. The final analysis was to be performed after all subjects had completed the study or discontinued study for any reason.

Table 3 shows the IRC-assessed overall response rate, the primary endpoint, in the primary analysis (data cutoff on January 27, 2023). The overall response rate [95% confidence interval (CI)] in Cohorts 1 and 2 combined was 97.0% [91.6%, 99.4%], with the lower limit of 95% CI exceeding the

3) Breyanzi was out of specification for [redacted] (in 2 subjects) and [redacted] (in 1 subject) due to the poor quality of the apheresis product.
4) Breyanzi infusion was postponed due to coronavirus disease (COVID-19). Since a repeated PET scan performed before Breyanzi infusion did not show a PET-positive lesion, Breyanzi infusion was cancelled.
5) Breyanzi was out of specification for [redacted] as an in-process control test due to the poor quality of the apheresis product.
6) Breyanzi was out of specification for [redacted] due to the poor quality of the apheresis product.

predefined overall response rate threshold (60%).[7)] The study protocol specified that an analysis of the overall response rate in Cohort 1 would be performed only if the lower limit of 95% CI of the overall response rate in Cohorts 1 and 2 combined exceeded the response rate threshold (60%). The overall response rate [95% CI] in Cohort 1 was 96.2% [87.0%, 99.5%], with the lower limit of 95% CI exceeding the predefined overall response rate threshold (50%).[8)] Furthermore, the overall response rate [95% CI] in Cohort 3 was 95.7% [78.1%, 99.9%], with the lower limit of 95% CI exceeding the predefined overall response rate threshold (50%).[9)] The multiplicity adjustment for hypothesis testing has not been made between the analysis of the primary endpoints in Cohorts 1 and 2 combined and the analysis of the primary endpoint in Cohort 3.

Table 3. Best response in the primary analysis
(IRC assessment, efficacy analysis set, data cutoff on January 27, 2023)

	n (%)			
	Cohort 1 (fourth-line and subsequent treatment)	Cohort 2 (third-line treatment)	Cohorts 1 and 2 combined (third-line and subsequent treatment)	Cohort 3 (second-line treatment)
	N = 53	N = 48	N = 101	N = 23[*1]
CR	49 (92.5)	46 (95.8)	95 (94.1)	22 (95.7)
PR	2 (3.8)	1 (2.1)	3 (3.0)	0
SD	1 (1.9)	0	1 (1.0)	0
PD	1 (1.9)	0	1 (1.0)	1 (4.3)
Unknown	0	1 (2.1)	1 (1.0)	0
Response (CR or PR)	51	47	98	22
Overall response rate [95% CI[*2]] (%)	96.2 [87.0, 99.5]	97.9 [88.9, 99.9]	97.0 [91.6, 99.4]	95.7 [78.1, 99.9]

*1 Of the 23 subjects in Cohort 3, 15 subjects met the criteria for POD24 (progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent), while 8 subjects did not meet the criteria for POD24 but met at least one of the modified groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.
*2 Clopper-Pearson method

Safety data were analyzed (data cutoff on January 27, 2023). Of 139 subjects enrolled, 14 subjects died (8 in Cohort 1, 5 in Cohort 2, and 1 in Cohort 3). Of the 14 subjects, one subject died before Breyanzi infusion (Cohort 1 [acute respiratory failure]) and another subject died after administration of OOS product (Cohort 2 [erythema multiforme]). After Breyanzi infusion, 12 deaths were reported. Most of the deaths (except 1 in Cohort 3) occurred ≥91 days after the treatment with Beyanzi. The causes of deaths in the 12 subjects were disease progression in 5 subjects (3 in Cohort 1 and 2 in Cohort 2), adverse events[10)] in 3 subjects (2 in Cohort 1 [acute myeloid leukaemia, progressive multifocal leukoencephalopathy] and 1 in Cohort 3 [haemophagocytic lymphohistiocytosis]), cardiac event in 1 subject (Cohort 1 [cardiac failure]), other causes in 2 subjects (Cohort 2 [coronavirus disease (COVID-19), COVID-19 pneumonia]), and newly identified malignancy in 1 subject (Cohort

7) Defined based on the overall response rates for phosphoinositide 3 kinase (PI3K) inhibitors, idelalisib, copanlisib, and duvelisib (54%, 59%, and 42%, respectively) in patients with relapsed or refractory FL in the third-line plus setting (*Blood.* 2014;124:1708, *J Clin Oncol.* 2017;35:3898-905, *J Clin Oncol.* 2019;37:912-22, etc.).

8) Since there were no reports on the overall response rate in the fourth-line and subsequent treatment for patients with relapsed or refractory FL, the overall response rate threshold for this cohort was defined based on the overall response rate threshold in Cohorts 1 and 2 combined, with the assumption that the overall response rate would decrease as the treatment progresses.

9) Since there was no report of the overall response rate in the second-line treatment for patients with high-risk relapsed or refractory FL, the overall response rate threshold that was at least comparable to the threshold in other cohorts in Study FOL-001 was selected, by taking into account the comprehensive clinical significance for this patient population.

10) From the start of LD chemotherapy to Day 90 after Breyanzi infusion, all adverse events were collected regardless of causal relationship. From Day 91 onward, only adverse events for which a causal relationship to the study procedure or Breyanzi could not be ruled out were to be collected. Death caused by cardiac event (1 subject) and death caused by new malignant tumor (1 subject) were reported on Day 91 after Breyanzi infusion and thereafter and considered to be unrelated to the study procedure or Breyanzi. The events were therefore not handled as adverse events.

1 [acute myeloid leukaemia]). A causal relationship to Breyanzi could not be ruled out in 1 subject in Cohort 1 (progressive multifocal leukoencephalopathy [11)]) and in 1 subject in Cohort 3 (haemophagocytic lymphohistiocytosis[12)]).

6.R Outline of the review conducted by PMDA

6.R.1 Efficacy

As a result of the review presented in the subsections below, PMDA concluded that Breyanzi was shown to have efficacy to a certain extent in patients with relapsed or refractory FL.

6.R.1.1 Efficacy endpoint and study design

The applicant's explanation about the reason for selecting the overall response rate as the primary endpoint of Study FOL-001:

The overall response rate is a primary endpoint that has been commonly used in clinical studies in patients with relapsed or refractory indolent non-Hodgkin lymphoma (NHL). To appropriately compare the data from Study FOL-001 with those that have been obtained in the past clinical studies and in clinical practice, the overall response rate was selected as the primary endpoint for Study FOL-001. The overall response rate is thought to allow prediction of clinical benefit, and therefore, it is reasonable to use the overall response rate, as well as the complete response rate, for evaluating the efficacy of drugs in patients with indolent NHL such as FL.

PMDA asked the applicant to explain the appropriateness of evaluating the efficacy and safety of Breyanzi in the second-line treatment for patients with high-risk relapsed or refractory FL in Cohort 3 of Study FOL-001, for the following reason:

In the confirmatory studies on the combination of lenalidomide and rituximab (genetical recombination) (hereinafter referred to as "rituximab") and the combination of obinutuzumab (genetical recombination) (hereinafter referred to as "obinutuzumab") and bendamustine (both combination regimens are described later as possible treatment options [see Section 6.R.3.1]), the efficacy and safety of these regimens were evaluated based on the results of randomized controlled clinical studies with the primary endpoint being progression free survival (PFS), etc., that directly reflects clinical efficacy; however, the efficacy and safety of Breyanzi were evaluated based on the results of the open-label uncontrolled clinical study with the primary endpoint being overall response rate.

The applicant's explanation:

In light of the following observations, etc., it is possible to evaluate the efficacy of Breyanzi in the second-line treatment for patients with high-risk relapsed or refractory FL based on the results in Cohort 3 of Study FOL-001, an open-label, uncontrolled study with the primary endpoint being overall response rate.

- As described above, the overall response rate is a useful endpoint that can potentially predict clinical benefit. In Study FOL-001, the lower limit of the 95% CI of the overall response rate, the

[11)] A 4[redacted]-year-old woman. Starting around Day 90 after Breyanzi infusion, Grade 1 tremor, Grade 2 fatigue, and Grade 1 muscular weakness occurred. The patient was diagnosed with Grade 4 progressive multifocal leukoencephalopathy on Day 127 and died on Day 190.

[12)] A 6[redacted]-year-old man. Grade 1 cytokine release syndrome (CRS) occurred on Day 2 after Breyanzi infusion and worsened to Grade 2 CRS on Day 5. The patient experienced Grade 4 haemophagocytic lymphohistiocytosis on Day 7 and died of the disease on Day 29. This event was possibly attributable to the reactivation of cytomegalovirus which was observed on Day 18.

primary endpoint, exceeded the pre-defined overall response rate threshold, and there is a consistency between the overall response rate and PFS and between the overall response rate and overall survival (OS).

- The baseline characteristics of the target patient populations and actually enrolled patients with FL in the confirmatory studies on the lenalidomide-rituximab combination and the obinutuzumab-bendamustine combination (AUGMENT study and GADOLIN study, respectively) differed from those in Cohort 3 of Study FOL-001 in terms of eligibility criteria including the following:
  (1) Both confirmatory studies included a certain number of patients with indolent NHL, in addition to those with FL.
  (2) In both confirmatory studies, the target treatment line was not limited to second-line treatment.
  (3) In both confirmatory studies, the study subjects were not limited to high-risk patients.
  (4) The AUGMENT study excluded patients refractory to rituximab.

  Although comparison of the results of Study FOL-001 and the confirmatory studies needs careful interpretation, the overall response rate, the complete response rate, PFS, and OS in Cohort 3 of Study FOL-001 were comparable to those in the lenalidomide-rituximab combination group of the AUGMENT study and those in the obinutuzumab-bendamustine combination group of the GADOLIN study.

- Since FL is a rare disease, the number of patients eligible for treatment with Breyanzi would be limited if its use were restricted to second-line treatment for high-risk patients. Given the favorable results of Study FOL-001, the conduct of a new randomized study comparing Breyanzi with conventional treatments seemed to be infeasible from both a patient enrollment and ethical standpoint.

PMDA's view:
The applicant's explanation about selecting the overall response rate as the primary endpoint is understandable. However, when evaluating the efficacy of treatment of relapsed or refractory FL, PFS and OS, which directly reflect the clinical usefulness of treatment, are also important. Therefore, PMDA evaluated the overall response rate as the primary endpoint and confirmed the outcomes of PFS and OS, as well.

The efficacy of Breyanzi in the second-line treatment of high-risk relapsed or refractory FL was investigated in an open-label, uncontrolled study (Study FOL-001). The study design is acceptable, taking into account that (1) the study subjects are high-risk patients with limited therapeutic options [see Section 6.R.3.1]; and (2) the overall response rate observed in Cohort 3 of Study FOL-001 was superior to the reported results of clinical studies using approved chemotherapy regimens [see Section 6.R.1.2].

6.R.1.2 Results of efficacy evaluation

The applicant's explanation about the efficacy of Breyanzi in the treatment of relapsed or refractory FL:

The primary analysis of Study FOL-001 (data cutoff on January 27, 2023) showed that the primary endpoint, the IRC-assessed overall response rate [95% CI], in the efficacy analysis set was 97.0% [91.6%, 99.4%] in Cohorts 1 and 2 combined, with the lower limit of 95% CI exceeding the pre-defined overall response rate threshold (60%). In light of the above results, an analysis was conducted on the overall response rate [95% CI] in Cohort 1, which was found to be 96.2% [87.0%, 99.5%], with the lower limit of 95% CI again exceeding the pre-defined overall response rate threshold (50%). In addition, the overall response rate [95% CI] in Cohort 3 was 95.7% [78.1%, 99.9%], with the lower limit of 95% CI also exceeding the pre-defined overall response rate threshold (50%).

The secondary endpoint, the IRC-assessed complete response rate [95% CI] was 94.1% [87.5%, 97.8%] in Cohorts 1 and 2 combined and 95.7% [78.1%, 99.9%] in Cohort 3.

The median PFS [95% CI] in the efficacy analysis set at the data cutoff of January 27, 2023 was not estimable (NE) [18.96, NE] months in Cohorts 1 and 2 combined and NE [20.21, NE] months in Cohort 3. Figure 1 shows the Kaplan-Meier curve for each cohort.

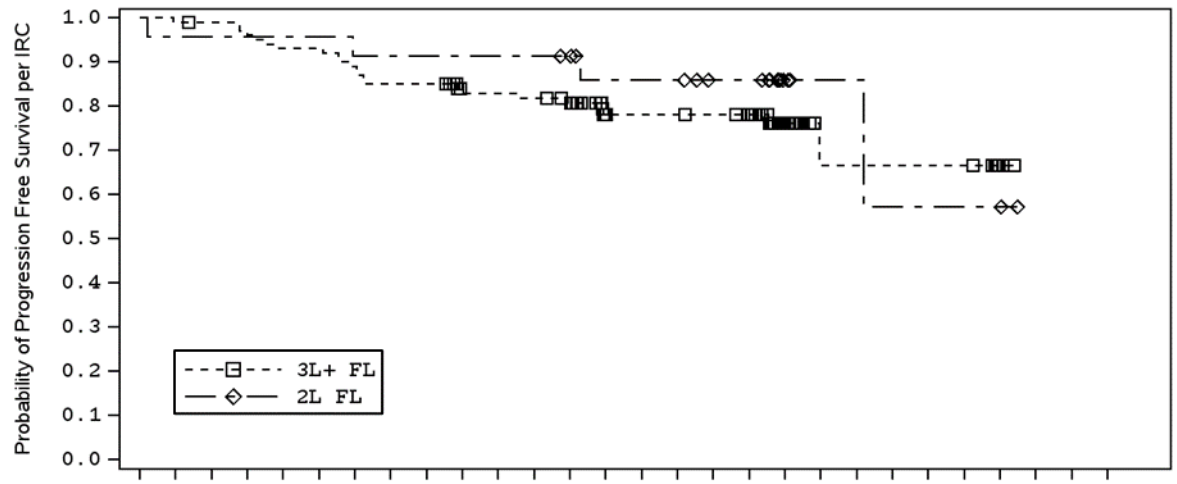


Figure 1. Kaplan-Meier curves of PFS in Cohorts 1 and 2 combined (the third-line and subsequent treatment [3L+]) and in Cohort 3 (the second-line treatment [2L]) (efficacy analysis set, data cutoff on January 27, 2023)

The median OS in the efficacy analysis set at the data cut-off of January 27, 2023 was not estimable because of the insufficient accrual of events. Figure 2 shows the Kaplan-Meier curve for each cohort.

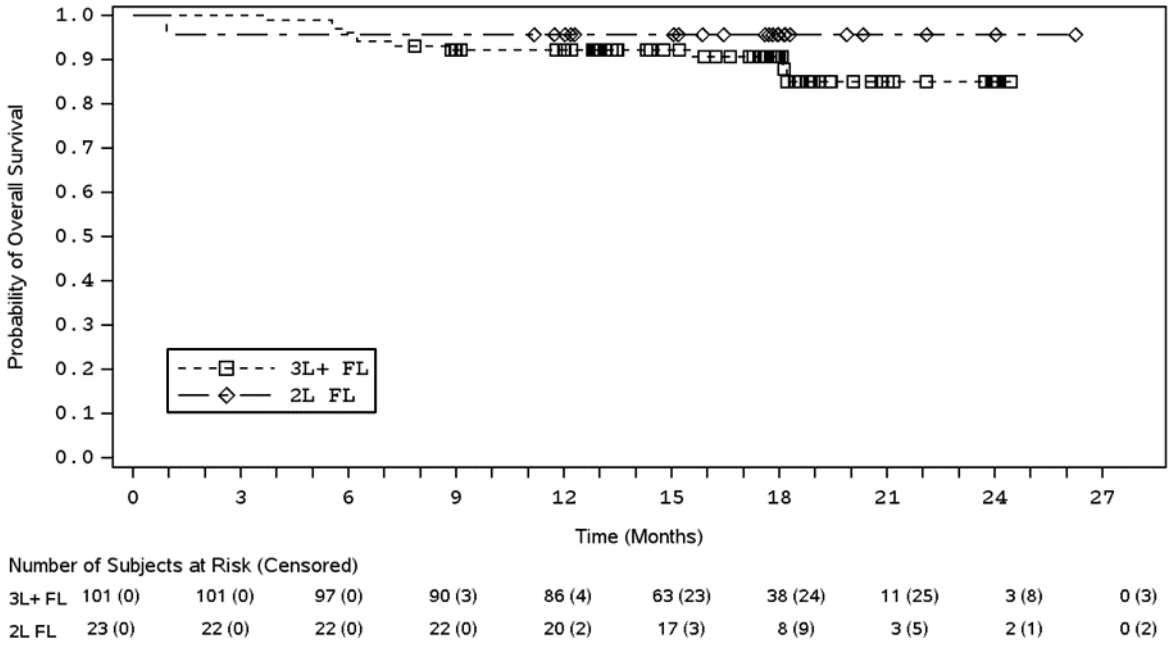


Figure 2. Kaplan-Meier curves of OS in Cohorts 1 and 2 combined (the third-line and subsequent treatment [3L+]) and in Cohort 3 (the second-line treatment [2L]) (efficacy analysis set, data cutoff on January 27, 2023)

Given the following points, the results of Study FOL-001 have demonstrated the efficacy of Breyanzi:

- According to the report of a clinical study on the currently approved chemotherapy regimen (*J Clin Oncol.* 2000;18:3135-43, *Br J Haematol.* 2000;109:81-8), the overall response rate ranged from 37% to 40% and the complete response rate was 11% in patients with relapsed or refractory FL in the third-line plus setting, revealing that the efficacy of Breyanzi achieved in Cohorts 1 and 2 combined tended to be superior to that observed with the approved chemotherapy. According to the meta-analysis including 20 studies published from 2014 to 2021 (*BMC Cancer.* 2023;23:74), the median PFS and OS were 9.78 and 56.57 months, respectively, indicating that there was no tendency toward shorter median PFS or OS in Cohorts 1 and 2 combined of Study FOL-001, albeit limitations to comparison with the external control.

- The literature on CD19 CAR T cell therapy as the third-line and subsequent treatment for relapsed or refractory FL was examined. Treatment with axicabtagene ciloleucel resulted in the overall response rate and the complete response rate of 94% and 79%, respectively, at a median follow-up period of 30.9 months (*Lancet Oncol.* 2022;23:91-103); and treatment with tisagenlecleucel resulted in the overall response rate and the complete response rate of 86% and 68%, respectively, at a median follow-up period of 29 months (*Nat Med.* 2022;28:325-32). In addition, treatment with mosunetuzumab, an anti-CD20/CD3 humanized monoclonal antibody with dual specificities, resulted in the overall response rate and the complete response rate of 78% and 60%, respectively, at a median follow-up period of 27 months (*Blood.* 2022;140 (Suppl 1):1467-70). The results obtained in Cohorts 1 and 2 combined of Study FOL-001 have been shown to be similar to those observed in the above studies, albeit limitations to comparisons with external controls.

- According to the reports of clinical studies on chemotherapy regimen and high-dose chemotherapy with hematopoietic stem cell transplant (HSCT) as the second-line treatment for patients with

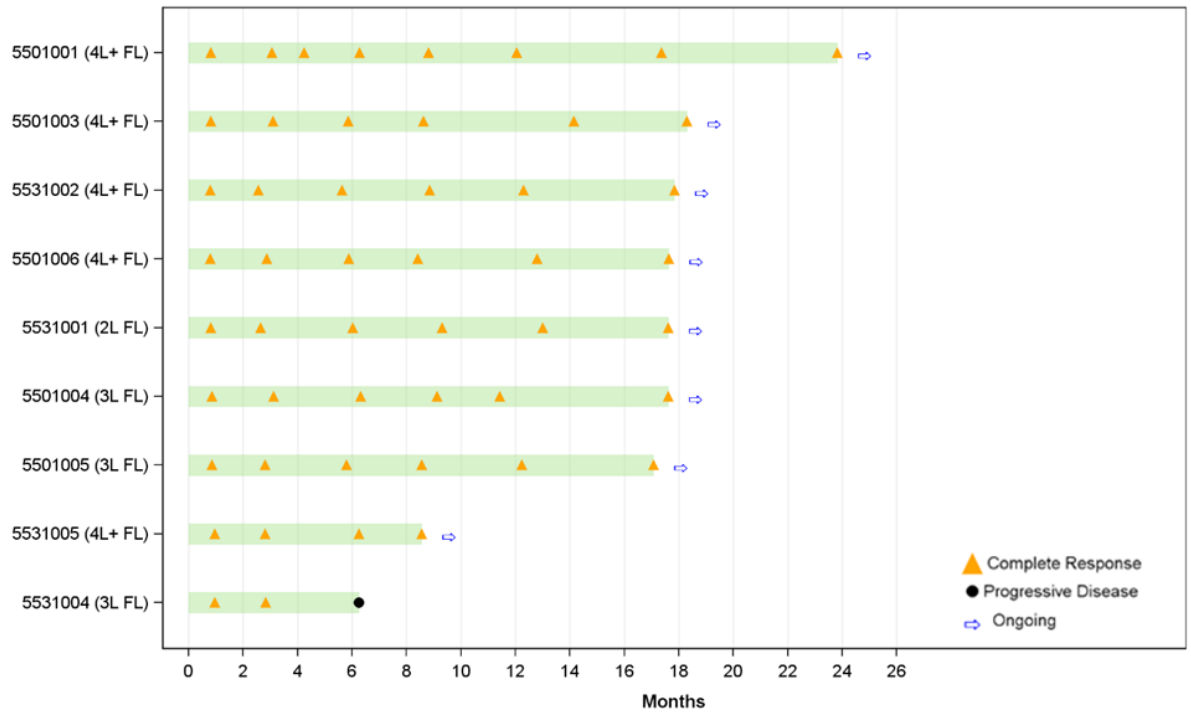
high-risk relapsed or refractory FL with POD24 (progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent), the overall response rate and the complete response rate ranged from 58% to 85% and from 29% to 55%, respectively (*J Clin Oncol.* 2022;40:16 (Suppl):7573). The median OS in the chemotherapy regimen ranged from 27.4 to 34.1 months (*Clin Lymphoma Myeloma Leuk.* 2019;19:300-9.e5), and the median OS in the high-dose chemotherapy with HSCT was not reached (*Eur J Haematol.* 2021;107:543-52). In the clinical study on the lenalidomide-rituximab combination regimen as the second-line and subsequent treatment for patients with high-risk relapsed or refractory FL with POD24 (MAGNIFY study), the overall response rate and the complete response rate were 65% and 32%, respectively, with a median PFS of 27.4 months (*Blood.* 2021;138 (Suppl 1):812). In view of these reports, the data[13)] obtained from Cohort 3 of Study FOL-001 demonstrate the clinical usefulness of Breyanzi despite limitations to the comparison with external controls.

In 9 Japanese patients (8 in Cohorts 1 and 2 combined, 1 in Cohort 3), the overall response rate [95% CI] was 100% [63.1%, 100.0%] in Cohorts 1 and 2 combined and 100% [2.5%, 100.0%] in Cohort 3, and the complete response rate [95% CI] was 100% [63.1%, 100.0%] in Cohorts 1 and 2 combined and 100% [2.5%, 100.0%] in Cohort 3, showing no clear difference between the Japanese population and the non-Japanese population.

Figure 3 shows changes over time in the treatment effect in individual Japanese patients. The median PFS [95% CI] was NE [6.24, NE] months in Cohorts 1 and 2 combined and not estimable in Cohort 3 due to insufficient accrual of events. The progression-free survival rate [95% CI] at Month 12 was 100% [100.0%, 100.0%]. The median OS was not estimable due to insufficient accrual of events. The overall survival rate [95% CI] at Month 18 was 100% [100.0%, 100.0%] both in Cohorts 1 and 2 combined and in Cohort 3.

The above results suggest sustained efficacy in the Japanese population as in the non-Japanese population, indicating the efficacy of Breyanzi in Japanese patients.

13) According to the data on PFS and OS in the efficacy analysis set at the data cutoff date of [redacted], 20[redacted], the progression-free survival rate [95% CI] at Month 30 was 82.6% [60.1%, 93.1%], and the overall survival rate [95% CI] at Month 36 was 95.7% [72.9%, 99.4%]. These data were submitted as reference.



4L+, fourth-line and subsequent treatment; 3L, third-line treatment; and 2L, second-line treatment

Figure 3. Swimmer's plot of Japanese population in Study FOL-001 (efficacy analysis set, data cut-off on January 27, 2023)

PMDA's view:

The applicant's above explanation is understandable. Taking the following into account, the results of Study FOL-001 have demonstrated that Breyanzi has efficacy to a certain extent in the treatment of patients with relapsed or refractory FL in the third-line plus setting and of patients with high-risk relapsed or refractory FL in the second-line setting.

- The lower limit of the 95% CI of the IRC-assessed overall response rate, the primary endpoint of Study FOL-001, exceeded the pre-defined overall response rate threshold in Cohorts 1 and 2 combined, in which the efficacy and safety of Breyanzi were assessed in patients with relapsed or refractory FL in the third-line plus setting. Although the multiplicity of hypothesis testing was not adjusted between the primary endpoint analysis in Cohorts 1 and 2 combined and the analysis in Cohort 3, the lower limit of the 95% CI of the IRC-assessed overall response rate, the primary endpoint, exceeded the pre-defined overall response rate threshold in Cohort 3 in which the efficacy and safety of Breyanzi were assessed in the second line treatment of patients with high-risk relapsed or refractory FL, demonstrating an increased response rate, compared with the reports of clinical studies on the approved chemotherapy regimens.

- In Study FOL-001, PFS did not tended to decrease, compared with the reports of clinical studies on the approved chemotherapy regimens, either in patients with relapsed or refractory FL in the third-line plus setting or in patients with high-risk relapsed or refractory FL in the second-line setting, despite limitations to comparison with external controls. In addition, the currently available data have not shown any tendency toward a decrease in OS compared with the OS reported in the clinical studies on approved chemotherapy regimens, despite limitations to comparison with external controls and the shorter follow-up period than that in the clinical studies.

- The currently available data including those on the overall response rate and the complete response rate suggest the efficacy of Breyanzi in Japanese patients as well, despite limitations to the comparison of PFS and OS in the Japanese population with those in the non-Japanese population because of the shorter follow-up period in the Japanese population than in the non-Japanese population.

6.R.2 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 FL are similar to those[14)] identified at the submission for the approved indications and that patients treated with Breyanzi should be carefully monitored for the occurrence of these adverse events, as in the case of the approved indication.

PMDA also concluded that Breyanzi is tolerable in patients with relapsed or refractory FL, 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 FL at a medical institution well-equipped for responding to these adverse events.

6.R.2.1 Safety profile of Breyanzi

The applicant's explanation about the safety of Breyanzi in patients with relapsed or refractory FL:
Table 4 shows the summary of the safety of Breyanzi in Study FOL-001 (data cutoff on January 27, 2023).

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

Table 4. Summary of safety (Study FOL-001, safety analysis set, data cutoff on January 27, 2023)

	n (%)				
	Cohort 1 (fourth-line and subsequent treatment) N = 59	Cohort 2 (third-line treatment) N = 48	Cohorts 1 and 2 combined (third-line and subsequent treatment) N = 107	Cohort 3 (second-line treatment) N = 23	Total N = 130
Any adverse event	58 (98.3)	47 (97.9)	105 (98.1)	23 (100)	128 (98.5)
Grade ≥3 adverse events	47 (79.7)	36 (75.0)	83 (77.6)	14 (60.9)	97 (74.6)
Serious adverse events	15 (25.4)	13 (27.1)	28 (26.2)	4 (17.4)	32 (24.6)
Adverse events resulting in death	0	0	0	1 (4.3)	1 (0.8)
Death	7 (11.9)	4 (8.3)	11 (10.3)	1 (4.3)	12 (9.2)
CRS[*1]	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
Grade ≥3 CRS[*1]	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Nervous system events[*2]	27 (45.8)	23 (47.9)	50 (46.7)	10 (43.5)	60 (46.2)
Grade ≥3 nervous system events[*2]	2 (3.4)	2 (4.2)	4 (3.7)	2 (8.7)	6 (4.6)
CAR T-associated neurotoxicity[*3]	8 (13.6)	8 (16.7)	16 (15.0)	4 (17.4)	20 (15.4)
Grade ≥3 CAR T cell-associated neurotoxicity[*3]	1 (1.7)	1 (2.1)	2 (1.9)	1 (4.3)	3 (2.3)
Infection[*4]	10 (16.9)	13 (27.1)	23 (21.5)	2 (8.7)	25 (19.2)
Grade ≥3 Infection[*4]	3 (5.1)	4 (8.3)	7 (6.5)	0	7 (5.4)
Cytopenia[*5]	47 (79.7)	36 (75.0)	83 (77.6)	14 (60.9)	97 (74.6)
Grade ≥3 cytopenia[*5]	38 (64.4)	32 (66.7)	70 (65.4)	12 (52.2)	82 (63.1)
Prolonged cytopenia[*6]	14 (23.7)	12 (25.0)	26 (24.3)	3 (13.0)	29 (22.3)
Macrophage activation syndrome[*7]	0	0	0	1 (4.3)	1 (0.8)
Hypogammaglobulinaemia[*8]	2 (3.4)	2 (4.2)	4 (3.7)	1 (4.3)	5 (3.8)
Secondary malignant tumor[*9]	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)

*1 Adverse events coded to "cytokine release syndrome" in the preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA)
*2 Adverse events coded to "nervous system disorders" or "psychiatric disorders" in the system organ class (SOC) of MedDRA
*3 Events considered Breyanzi-associated neurotoxicity by the investigator
*4 Adverse events coded to "infections and infestations" in MedDRA SOC
*5 Events listed in Table 5
*6 Grade ≥3 cytopenia (the following laboratory abnormalities: Haemoglobin decreased, neutrophil count decreased, or platelet count decreased) observed at hospital visit on Day 29 after Breyanzi infusion
*7 Adverse events coded to "haemophagocytic lymphohistiocytosis" in MedDRA PT
*8 Adverse events coded to "blood immunoglobulin A decreased," "blood immunoglobulin G decreased," "blood immunoglobulin M decreased," "hypogammaglobulinaemia," "immunoglobulins decreased," "selective IgA immunodeficiency," "selective IgG subclass deficiency," or "selective IgM immunodeficiency" in MedDRA PT
*9 Adverse events which were coded to "premalignant disorders" or "malignancies" in MedDRA Standardized MedDRA Query (SMQ) and were then identified by the clinical review of the assessment committee.

Table 5. List of events collected as cytopenia

Classification	MedDRA PT (MedDRA version 25.1)
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

Table 6 shows the summary of the safety of Breyanzi in the Japanese and the non-Japanese populations in Study FOL-001. There were no serious adverse events or adverse events resulting in death in the Japanese population.

Table 6. Summary of safety of Breyanzi in Japanese and non-Japanese patients (Study FOL-001, safety analysis set, data cutoff on January 27, 2023)

	n (%)					
	Cohorts 1 and 2 combined (third-line and subsequent treatment)		Cohort 3 (second line treatment)		Total	
	Japanese population N = 9	Non-Japanese population N = 98	Japanese population N = 1	Non-Japanese population N = 22	Japanese population N = 10	Non-Japanese population N = 120
Any adverse event	9 (100)	96 (98.0)	1 (100)	22 (100)	10 (100)	118 (98.3)
Grade ≥3 adverse events	9 (100)	74 (75.5)	0	14 (63.6)	9 (90.0)	88 (73.3)
Serious adverse events	0	28 (28.6)	0	4 (18.2)	0	32 (26.7)
Adverse events resulting in death	0	0	0	1 (4.5)	0	1 (0.8)
Death	0	11 (11.2)	0	1 (4.5)	0	12 (10.0)
CRS[*1]	3 (33.3)	60 (61.2)	0	12 (54.5)	3 (30.0)	72 (60.0)
Grade ≥3 CRS[*1]	0	1 (1.0)	0	0	0	1 (0.8)
Nervous system events[*2]	3 (33.3)	47 (48.0)	0	10 (45.5)	3 (30.0)	57 (47.5)
Grade ≥3 nervous system events[*2]	0	4 (4.1)	0	2 (9.1)	0	6 (5.0)
CAR T-associated neurotoxicity[*3]	1 (11.1)	15 (15.3)	0	4 (18.2)	1 (10.0)	19 (15.8)
Grade ≥3 CAR T cell-associated neurotoxicity[*3]	0	2 (2.0)	0	1 (4.5)	0	3 (2.5)
Infection[*4]	0	23 (23.5)	0	2 (9.1)	0	25 (20.8)
Grade ≥3 Infection[*4]	0	7 (7.1)	0	0	0	7 (5.8)
Cytopenia[*5]	9 (100)	74 (75.5)	0	14 (63.6)	9 (90.0)	88 (77.3)
Grade ≥3 cytopenia[*5]	7 (77.8)	63 (64.3)	0	12 (54.5)	7 (70.0)	75 (62.5)
Prolonged cytopenia[*6]	1 (11.1)	25 (25.5)	0	3 (13.6)	1 (10.0)	28 (23.3)
Macrophage activation syndrome[*7]	0	0	0	1 (4.5)	0	1 (0.8)
Hypogammaglobulinaemia[*8]	1 (11.1)	3 (3.1)	1 (100)	0	2 (20.0)	3 (2.5)
Secondary malignant tumor[*9]	0	1 (1.0)	0	1 (4.5)	0	2 (1.7)

*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
*4 Adverse events coded to "Infections and infestations" in MedDRA SOC
*5 Events listed in Table 5
*6 Grade ≥3 cytopenia (the following laboratory abnormalities: Haemoglobin decreased, neutrophil count decreased, or platelet count decreased) observed at hospital visit on Day 29 after Breyanzi infusion
*7 Adverse events coded to "haemophagocytic lymphohistiocytosis" in MedDRA PT
*8 Adverse events coded to "blood immunoglobulin A decreased," "blood immunoglobulin G decreased," "blood immunoglobulin M decreased," "hypogammaglobulinaemia," "immunoglobulins decreased," "selective IgA immunodeficiency," "selective IgG subclass deficiency," or "selective IgM immunodeficiency" in MedDRA PT
*9 Adverse events which were coded to "premalignant disorders" or "malignancies" in MedDRA SMQ and were then identified by the clinical review of the assessment committee.

Table 7 shows all-grade or Grade ≥3 adverse events with a ≥20% higher incidence in the Japanese population than in the non-Japanese population.

Table 7. Adverse events with ≥20% higher incidence in the Japanese population than in the non-Japanese population (Study FOL-001, safety analysis set, data cutoff on January 27, 2023)

PT (MedDRA/J ver.25.1)	n (%) Total	
	Japanese population N = 10	Non-Japanese population N = 120
All Grade adverse events	10 (100)	118 (98.3)
Lymphopenia	6 (60.0)	14 (11.7)
Alanine aminotransferase increased	3 (30.0)	7 (5.8)
Aspartate aminotransferase increased	3 (30.0)	5 (4.2)
Neutrophil count decreased	3 (30.0)	3 (2.5)
Grade ≥3 adverse events	9 (90.0)	88 (73.3)
Lymphopenia	6 (60.0)	11 (9.2)
Neutrophil count decreased	3 (30.0)	3 (2.5)

Despite the limitations to the comparison of the safety between the Japanese population and the non-Japanese population because of the limited number of Japanese patients, there were no clear differences in the safety profile of Breyanzi between the Japanese and the non-Japanese populations.

In view of the fact that the dosage regimen or method of use of Breyanzi employed in Study FOL-001 in patients with relapsed or refractory FL was similar to those in Studies JCAR017-BCM-001 (Study BCM-001) and JCAR017-BCM-003 (Study BCM-003) in patients with relapsed or refractory LBCL, the applicant provided the following explanation about the differences in the safety profile of Breyanzi between the treatment of relapsed or refractory FL and the treatment of LBCL that is the approved indication:

Table 8 shows the summary of the safety of Breyanzi in Study FOL-001 in patients with relapsed or refractory FL, and clinical studies in patients with relapsed or refractory LBCL, the approved indication (DLBCL cohort[15)] of Study 017001 in patients with LBCL in the third-line plus setting, the Breyanzi group of Study BCM-003[16)] in patients with LBCL in the second-line setting, and Study 017006[17)]). There were no clear differences between the safety profile of Breyanzi confirmed in Study FOL-001 and the safety profile of Breyanzi observed in patients with LBCL, the approved indication.

15) An open-label, uncontrolled study to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory B cell NHL. Breyanzi was intravenously infused (a) as a single dose at a target dose of 50×10^6 anti-CD19 CAR T cells (25×10^6 CD8-positive T cells and 25×10^6 CD4-positive T cells), 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells and 50×10^6 CD4-positive T cells), or 150×10^6 anti-CD19 CAR T cells (75×10^6 CD8-positive T cells and 75×10^6 CD4-positive T cells), or (b) at a dose of 50×10^6 CAR-positive viable T cells, followed by the re-administration of the same dose 14 days later (Review report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021).

16) An open-label, randomized study to assess the efficacy and safety of Breyanzi versus the standard therapy in patients with relapsed or refractory aggressive B-cell NHL eligible for autologous HSCT. Breyanzi was administered as a single intravenous infusion at a target dose of 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells and 50×10^6 CD4-positive T cells) (Review report on Breyanzi Suspension for Intravenous Infusion, dated November 24, 2022).

17) An open-label, uncontrolled study to investigate the efficacy and safety of Breyanzi in patients with relapsed or refractory aggressive B cell NHL ineligible for autologous HSCT. Breyanzi was intravenously infused as a single dose at a target dose of 100×10^6 anti-CD19 CAR T cells (50×10^6 CD8-positive T cells and 50×10^6 CD4-positive T cells) (Review report on Breyanzi Suspension for Intravenous Infusion, dated November 24, 2022).

Table 8. Comparison of safety of Briyanzi between a clinical study in patients with FL and those in patients with LBCL (Study FOL-001, DLBCL cohort of Study 017001, Breyanzi group in Study BCM-003, Study 017006,[*1] safety analysis sets)

	n (%)	
	Clinical study in patients with FL	Clinical studies in patients with LBCL
	Entire population of Study FOL-001	DLBCL cohort of Study 017001 Breyanzi group in Study BCM-003 Study 017006
	(second-line and subsequent treatment) N = 130	(second-line and subsequent treatment) N = 418
Death	12 (9.2)	143 (34.2)
Death due to disease progression	5 (3.8)	116 (27.8)
Death due to adverse events	3 (2.3)	14 (3.3)
Any adverse event	128 (98.5)	412 (98.6)
Grade ≥3 adverse events	97 (74.6)	337 (80.6)
Serious adverse events	32 (24.6)	176 (42.1)
Adverse events resulting in death	1 (0.8)	13 (3.1)
CRS[*2]	75 (57.7)	190 (45.5)
Grade ≥3 CRS[*2]	1 (0.8)	13 (3.1)
Nervous system events[*3]	60 (46.2)	290 (69.4)
Grade ≥3 nervous system events[*3]	6 (4.6)	57 (13.6)
CAR T-associated neurotoxicity[*4]	20 (15.4)	136 (32.5)
Grade ≥3 CAR T cell-associated neurotoxicity[*4]	3 (2.3)	42 (10.0)
Infection[*5]	25 (19.2)	150 (35.9)
Grade ≥3 Infection[*5]	7 (5.4)	50 (12.0)
Cytopenia[*6]	97 (74.6)	325 (77.8)
Grade ≥3 cytopenia[*6]	82 (63.1)	305 (73.0)
Prolonged cytopenia[*7]	29 (22.3)	157 (37.6)
Macrophage activation syndrome[*8]	1 (0.8)	1 (0.2)
Tumour lysis syndrome[*9]	0	2 (0.5)
Hypogammaglobulinaemia[*10]	5 (3.8)	47 (11.2)
Secondary malignant tumor[*11]	2 (1.5)	5 (1.2)

*1 Study FOL-001 (data cutoff on January 27, 2023); Study 017001 (data cutoff on April 12, 2019); Breyanzi group in Study BCM-003 (data cutoff on March 8, 2021); and Study 017006 (data cutoff on May 28, 2021)
*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
*5 Adverse events coded to "infections and infestations" in MedDRA SOC
*6 Events listed in Table 5
*7 Grade ≥3 cytopenia (the following laboratory abnormalities: Haemoglobin decreased, neutrophil count decreased, or platelet count decreased) observed at hospital visit on Day 29 after Breyanzi infusion
*8 Adverse events coded to "haemophagocytic lymphohistiocytosis" in MedDRA PT
*9 Adverse events coded to "tumour lysis syndrome" in MedDRA PT
*10 Adverse events coded to "blood immunoglobulin A decreased," "blood immunoglobulin G decreased," "blood immunoglobulin M decreased," "hypogammaglobulinaemia," "immunoglobulins decreased," "selective IgA immunodeficiency," "selective IgG subclass deficiency," or "selective IgM immunodeficiency in MedDRA PT
*11 Adverse events which were coded to "premalignant disorders" or "malignancies" in MedDRA SMQ and were then identified by the clinical review of the assessment committee.

PMDA's view:

Adverse events did not tend to occur more frequently in Study FOL-001 than in clinical studies in patients with LBCL (the approved indication), whereas serious adverse events such as cytokine release syndrome (CRS) occurred after Breyanzi infusion as in studies in patients with LBCL. The patient should be monitored very closely after Breyanzi infusion, and adverse events, if any, should be treated by a multidisciplinary approach. Adverse events should be more carefully managed in Japanese patients because of the higher incidence of cytopenia in the Japanese population than in the non-Japanese population, although the limited experience with the use of Breyanzi in Japanese patents precludes stringent comparison of the safety of Breyanzi between Japanese and non-Japanese patients.

All of the above-mentioned adverse events are known adverse events associated with the use of Breyanzi. The package insert advises that patients should undergo hematology tests periodically. PMDA considers that Breyanzi is tolerable in patients with relapsed or refractory FL, 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 FL at a medical institution well-equipped for responding to these adverse events.

6.R.3 Clinical positioning and indications or performance

The proposed "Indications or Performance" of Breyanzi at the submission of the partial change application was as follows:

Indications or Performance (Underline denotes addition to 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

Relapsed or refractory follicular lymphoma <u>(Grade 1, 2, 3A, or 3B)</u>

Breyanzi, however, is intended only for patients with no history of the transfusion of chimeric antigen receptor-positive T cells targeting CD19 antigen.

The "Precautions Concerning Indications or Performance" section included the following description.

Precautions Concerning Indications or Performance (Strikethrough denotes deletions 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.~~
- 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.1 Efficacy" and "6.R.2 Safety," and the review presented below, the "Indications or Performance" section should be specified as shown below and the "Precautions Concerning Dosage and Administration" 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

Relapsed or refractory follicular lymphoma ~~(Grade 1, 2, 3A, or 3B)~~

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.3.1 Clinical positioning and target population of Breyanzi

While the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell lymphomas (hereinafter referred to as "NCCN Guidelines") recommend anti-CD19 CAR T cell products (axicabtagene ciloleucel and tisagenlecleucel) as treatment options for the third-line and subsequent therapy for patients with relapsed or refractory FL, Breyanzi is not included in the list.

Clinical practice guidelines

NCCN Guidelines (v6.2023): Administration of anti-CD19 CAR T cell products (axicabtagene ciloleucel and tisagenlecleucel) is recommended for the treatment of relapsed or refractory FL following the completion of second-line treatment (Category 2A[18)]).

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

FL initially shows sensitivity to various chemotherapies. In patients with FL relapsed after or refractory to first-line treatment, however, the disease exhibits a persistent pattern of relapse with decreased sensitivity to chemotherapy, leading to a poor outcome. Especially, in patients with FL in the third-line plus setting, disease progression leads to reduced PFS and OS (*Haematologica.* 2023;108:822-32, *Lancet Hematol.* 2022;9:e289-e300). In Japan, there is no standard of care treatment for patients with relapsed or refractory FL, with a fewer number of approved drugs for treatment of relapsed or refractory FL compared to other countries, resulting in limited treatment options available. In August 2022, tisagenlecleucel, a CAR T cell therapy, was granted additional approval for use as a third-line and subsequent treatment for relapsed or refractory FL. The CAR T cell therapy, however, cannot be considered an established treatment because it has only limited post-marketing experience so far.

In addition, the prognosis is poorer in patients with high-risk relapsed or refractory FL with POD24 in the second-line setting than in patients without these risk factors (*J Clin Oncol.* 2022;4016(Suppl): 7573). In the NCCN Guidelines (v6.2023), the duration of response to first-line treatment is considered an important factor in choosing second-line treatment. The Guidelines state that treatment with a lenalidomide-based regimen (such as the lenalidomide-rituximab combination), novel approaches including clinical studies, or high-dose chemotherapy with HSCT should be considered for FL patients with POD24 who have experienced disease progression within 2 years following the completion of first-line treatment. This indicates limited treatment options available. If FL patients without POD24 who have symptomatic disease or high tumor burden according to criteria such as the groupe d'Etude des Lymphomes Folliculaires (GELF) are not refractory to first-line chemotherapy, changing rituximab or obinutuzumab in the first-line regimen (such as a combination regimen with obinutuzumab and bendamustine) or switching to a combination regimen with lenalidomide and rituximab may be considered as second-line treatment options involving non-cross-resistant

[18)] Based upon low-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

chemotherapy. If the patient is refractory to first-line treatment, repeated use of these chemotherapies is not ideal. There are no clearly recommended options for second-line treatment.

Under such circumstances, Study FOL-001 demonstrated the efficacy and safety of Breyanzi both in patients with relapsed or refractory FL (Grade 1, 2, or 3A) in the third-line plus setting and in patients with high-risk relapsed or refractory FL (Grade 1, 2, or 3A) in the second-line setting. The study results suggest that Breyanzi serves as a new treatment option for these patient populations. In order to add FL (Grade 1, 2, or 3A) to the approved indication (FL3B) of Breyanzi, the "Indications or Performance" of Breyanzi will be "relapsed or refractory follicular lymphoma (Grade 1, 2, 3A, or 3B)." Further, the following description in the "Precautions Concerning Indications or Performance" section will be deleted: Breyanzi should be administered to patients with clinical condition of Grade 3B FL assessed by a well-experienced pathologist.

Patients enrolled in Cohort 3 of Study FOL-001 were those with high-risk relapsed or refractory FL. This fact could provide important information in assessing the eligibility of patients for treatment with Breyanzi. Accordingly, the fact that the study subjects were high-risk patients meeting POD24 or GELF criteria will be included in the "Clinical Studies" section of the package insert. Further, the "Precautions Concerning Indication or Performance" section will specify that eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on the knowledge from the "Clinical Studies" section.

PMDA's view:
It is acceptable to include the description "FL (Grade 1, 2, or 3A)" in the "Indications or Performance" of Breyanzi based on the results of Study FOL-001. Since the approved indication (FL3B) will be expanded to include FL (Grade 1, 2, or 3A), there is no need to specify the grade. The description "(Grade 1, 2, 3A, or 3B)" should be removed.

Given that the extremely high risk of serious adverse events associated with the infusion of Breyanzi, such as CRS, Breyanzi is not recommended for use in patient populations other than those included in Study FOL-001. The "Clinical Studies" section of the package insert should clarify the prior therapies of patients treated in Study FOL-001, including not only patients with high-risk relapsed or refractory FL in Cohort 3 but also patient populations in Cohorts 1 and 2 combined, and the "Precautions Concerning Indication or Performance" section should clearly state that eligible patients must be selected by physicians with a full understanding of the efficacy and safety of Breyanzi based on the knowledge from the "Clinical Studies" section.

6.R.4 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 the approved "Dosage and Administration or Method of Use."

The applicant's explanation about the rationale for the proposed "Dosage and Administration or Method of Use" for Breyanzi:
In Study FOL-001, Breyanzi was administered according to the approved "Dosage and Administration or Method of Use." The study demonstrated the efficacy and safety of Breyanzi. Accordingly, the same "Dosage and Administration or Method of Use" as that for the approved indications was selected for the treatment of patients with relapsed or refractory FL.

Based on the reviews presented in Sections "6.R.1 Efficacy" and "6.R.2 Safety," PMDA concluded that the same "Dosage and Administration or Method of Use" as that for the approved indication can be selected for the treatment of patients with relapsed or refractory FL.

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

The applicant's explanation about the post-marketing surveillance plan for Breyanzi:
In the ongoing post-marketing database surveillance[19)] for all patients treated with Breyanzi under the approved indications, patients with FL3B are already identified as a target patient population. In addition, the safety profile of Breyanzi in patients with relapsed or refractory FL in Study FOL-001 was shown to be similar to that of Breyanzi under the approved indications [see Section 6.R.2.1]. For the above reasons, patients with relapsed or refractory FL (Grade 1, 2, or 3A) will be included in the target patient populations of the database surveillance.

Since reports suggestive of the association of "brain edema" listed in the safety specification with nervous system events have been accrued, data on brain edema will be collected and analyzed under the category of the "nervous system events" in the safety specification. No other change will be made to the safety specification, which will include the following: "CRS," "nervous system events," "infection," "hypogammaglobulinemia," "macrophage activation syndrome (hemophagocytic lymphohistiocytosis)," "tumour lysis syndrome," "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)," "effect on pregnancy and breast-feeding," and "long-term safety."

The surveillance is planned to monitor 100 patients with FL (Grade 1, 2, or 3A) in addition to the initially planned number of patients, taking account of the following assumption:

- Judging from data on the post-marketing use of Breyanzi, approximately 96 patients are expected to receive Breyanzi for the treatment of FL (Grade 1, 2, or 3A) (during 3 years after the approval of the present partial change application).
- A total of 95 patients will be needed to identify at least 1 patient showing an adverse event that occurs at the incidence of 3.1% (the incidence of secondary carcinogenesis which occurred at the lowest incidence in Study FOL-001, among the events listed in the safety specification) with 95% probability.

19) Safety specifications:
CRS, nervous system events, infection, hypogammaglobulinemia, macrophage activation syndrome (hemophagocytic lymphohistiocytosis), tumour lysis syndrome, 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.

The maximum follow-up period is 8 years to evaluate each of the specifications in this surveillance.

PMDA's view:
Because of the extremely limited information on the safety of Breyanzi in Japanese patients with FL, the applicant should conduct surveillance in all patients with FL treated with Breyanzi in the post-marketing setting to collect information and promptly communicate the safety information obtained to healthcare professionals.

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

Details of the post-marketing surveillance will be finalized, taking account of comments from the expert advisors in the Expert Discussion on the safety evaluation 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 in the subsections below.

8.1 Global phase II study (Study FOL-001)

Adverse events were observed in 58 of 59 subjects (98.3%), 47 of 48 subjects (97.9%), and 23 of 23 subjects (100%), respectively, in Cohort 1 (fourth-line and subsequent treatment), Cohort 2 (third-line treatment), and Cohort 3 (second-line treatment). Adverse events, for which a causal relationship to Breyanzi could not be ruled out, were observed in 54 of 59 subjects (91.5%), 41 of 48 subjects (85.4%), and 19 of 23 subjects (82.6%), respectively. Table 9 shows adverse events reported by ≥10% of subjects in any group.

Table 9. Adverse events reported by ≥10% of subjects in any group (Study FOL-001)

SOC PT (MedDRA ver.25.1)	n (%)					
	Cohort 1 (fourth-line and subsequent treatment) N = 59		Cohort 2 (third-line treatment) N = 48		Cohort 3 (second-line treatment) N = 23	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	58 (98.3)	47 (79.7)	47 (97.9)	36 (75.0)	23 (100)	14 (60.9)
Blood and lymphatic system disorders						
Neutropenia	38 (64.4)	35 (59.3)	33 (68.8)	29 (60.4)	14 (60.9)	12 (52.2)
Anaemia	25 (42.4)	6 (10.2)	19 (39.6)	6 (12.5)	5 (21.7)	1 (4.3)
Thrombocytopenia	18 (30.5)	4 (6.8)	12 (25.0)	8 (16.7)	3 (13.0)	1 (4.3)
Leukopenia	8 (13.6)	7 (11.9)	6 (12.5)	4 (8.3)	4 (17.4)	4 (17.4)
Lymphopenia	8 (13.6)	7 (11.9)	7 (14.6)	6 (12.5)	5 (21.7)	4 (17.4)
Immune system disorders						
CRS	35 (59.3)	1 (1.7)	28 (58.3)	0	12 (52.2)	0
Gastrointestinal disorders						
Constipation	13 (22.0)	0	9 (18.8)	0	4 (17.4)	0
Diarrhoea	9 (15.3)	0	7 (14.6)	0	6 (26.1)	0
Nausea	7 (11.9)	0	3 (6.3)	0	2 (8.7)	0
Abdominal pain	0	0	4 (8.3)	0	5 (21.7)	1 (4.3)
General disorders and administration site conditions						
Pyrexia	10 (16.9)	0	11 (22.9)	0	2 (8.7)	0
Asthenia	9 (15.3)	0	5 (10.4)	0	2 (8.7)	0
Fatigue	9 (15.3)	0	3 (6.3)	0	7 (30.4)	0
Nervous system disorders						
Headache	19 (32.2)	0	11 (22.9)	0	8 (34.8)	0
Tremor	9 (15.3)	0	7 (14.6)	0	2 (8.7)	0
Aphasia	6 (10.2)	1 (1.7)	1 (2.1)	0	2 (8.7)	0
Dizziness	2 (3.4)	0	1 (2.1)	0	3 (13.0)	0
Musculoskeletal and connective tissue disorders						
Back pain	5 (8.5)	0	0	0	4 (17.4)	0
Arthralgia	4 (6.8)	0	5 (10.4)	0	1 (4.3)	0
Investigations						
Blood creatinine increased	1 (1.7)	0	2 (4.2)	0	3 (13.0)	0
Metabolism and nutrition disorders						
Hypokalaemia	7 (11.9)	0	1 (2.1)	0	1 (4.3)	0
Vascular disorders						
Hypotension	6 (10.2)	0	3 (6.3)	0	1 (4.3)	0
Respiratory, thoracic and mediastinal disorders						
Cough	6 (10.2)	0	1 (2.1)	0	2 (8.7)	0

Serious adverse events were observed in 15 of 59 subjects (25.4%), 13 of 48 subjects (27.1%), and 4 of 23 subjects (17.4%) in Cohort 1 (fourth-line and subsequent treatment), Cohort 2 (third-line treatment), and Cohort 3 (second-line treatment), respectively. Serious adverse events observed in ≥2 subjects in Cohort 1 (fourth-line and subsequent treatment) were CRS in 7 subjects, aphasia in 4 subjects, tremor in 2 subjects, confusional state in 2 subjects, and febrile neutropenia in 2 subjects. A causal relationship to Breyanzi could not be ruled out for CRS in 7 subjects, aphasia in 4 subjects, tremor in 2 subjects, confusional state in 2 subjects, and febrile neutropenia in 1 subject. Serious adverse events observed in ≥2 subjects in Cohort 2 (third-line treatment) were CRS in 4 subjects, febrile neutropenia in 2 subjects, and pyrexia in 2 subjects. A causal relationship to Breyanzi could not be ruled out for any of them. Serious adverse events observed in Cohort 3 (second-line treatment) were CRS, allergy to immunoglobulin therapy, hemophagocytic lymphohistiocytosis, aphasia, feeling abnormal, and adenocarcinoma of colon in 1 subject each. A causal relationship to Breyanzi could not be ruled out for CRS, hemophagocytic lymphohistiocytosis, aphasia, and feeling abnormal.

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

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

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

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

The new regenerative medical product application data (CTD 5.3.5.2-1) 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.

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 follicular lymphoma," 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 FL.

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

Review Report (2)

July 3, 2024

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	November 20, 2023

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

As a result of the review in Section "6.R.1 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of Breyanzi has been demonstrated in the treatment of patients with relapsed or refractory FL in the third-line plus setting and of patients with high-risk relapsed or refractory FL in the second-line setting because the IRC-assessed overall response rate defined as the primary efficacy endpoint in Study FOL-001 (Cohorts 1 and 2 combined, and Cohort 3) in patients with relapsed or refractory FL was greater than the predefined efficacy threshold.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the review in Section "6.R.2 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention during the use of Breyanzi in patients with relapsed or refractory FL are the same as those[20)] identified in the review of the initial application, and that patients treated with Breyanzi should be carefully monitored for the occurrence of these adverse events, as in the case of the approved indication.

[20)] CRS, hemophagocytic lymphohistiocytosis, nerve disorder, infection, bone marrow depression, hypersensitivity, hypogammaglobulinaemia, and tumour lysis syndrome (Review report on Breyanzi Suspension for Intravenous Infusion, dated February 2, 2021)

PMDA has 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 FL 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.3 Clinical positioning and indications or performance" of the Review Report (1), PMDA has concluded that the "Indications or Performance" and "Precautions Concerning Indications or Performance" sections should be described as follows, 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 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.

Precautions Concerning Indications or Performance

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 the applicant's response.

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.4 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 for the initial application.

The above conclusion of PMDA was 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 10 because the safety profile of Breyanzi in patients with relapsed or refractory FL is similar to that for the approved

indication. The applicant plans to expand the target patient populations for the post-marketing database surveillance planned at the initial approval of Breyanzi to include patients with relapsed or refractory FL (Grade 1, 2, or 3A). The surveillance will cover all patients treated with Breyanzi.

PMDA has concluded that the post-marketing surveillance plan as proposed by the applicant is acceptable, as reviewed in Section "7 Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Table 10. Outline of the 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	400 patients (300 patients with LBCL and FL3B and 100 patients with FL [Grade 1, 2, or 3A]) A total of 100 patients with FL (Grade 1, 2, or 3A) receiving Breyanzi after the date of approval of the present application will be added.
Main survey items	Safety specification CRS, nervous system events,* infection, hypogammaglobulinemia, macrophage activation syndrome (hemophagocytic lymphohistiocytosis), tumour lysis syndrome, 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, effect on pregnancy and breast-feeding, and long-term safety Efficacy LBCL and FL3B: Best response, PFS, OS, event-free survival (EFS) FL (Grade 1, 2, or 3A): Best response, PFS, OS

* Since reports suggestive of the association of "brain edema" listed in the safety specification with nervous system events have been accrued, data on brain edema will be collected and analyzed under the category of "nervous system events" in the safety specification.

2. Overall Evaluation

As a result of the above 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 refined as below, with the following approval conditions, based on the premise that the provision of cautionary advice via the package insert and the dissemination of information on proper use of the product are appropriately implemented in the post-marketing setting. Because Breyanzi is designated as an orphan regenerative medical product with the intended indications or performance for the treatment of "follicular lymphoma (Grade 1, 2, or 3A) and marginal zone lymphoma," the re-examination period should be 10 years for the indication or performance added in the present application.

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 ~~(Grade 1, 2, 3A, or 3B)~~

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

Breyanzi	Breyanzi Suspension for Intravenous Infusion
CAR	chimeric antigen receptor
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
COVID-19	Coronavirus disease
CR	complete response
CRS	cytokine release syndrome
Cyclophosphamide	Cyclophosphamide Hydrate
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EGFRt	Truncated epidermal growth factor receptor
FL	follicular lymphoma
FL3B	follicular lymphoma grade 3B
Fludarabine	Fludarabine Phosphate
GELF	groupe d'Etude des Lymphomes Folliculaires
HGBCL	high grade B-cell lymphoma
HSCT	hematopoietic stem cell transplant
Ig	Immunoglobulin
IRC	Independent Response Committee
LBCL	large B-cell lymphoma
LD chemotherapy	lymphodepleting chemotherapy
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	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
NE	not estimable
NHL	non-Hodgkin lymphoma
Obinutuzumab	Obinutuzumab (Genetical Recombination)
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PI3K	phosphoinositide 3 kinase
PMBCL	primary mediastinal large B-cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
POD24	Progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent
PR	partial response
PS	performance status
PT	preferred term
Rituximab	Rituximab (Genetical Recombination)
SD	stable disease
SMQ	Standardized MedDRA Query
SOC	system organ class
Study BCM-001	Study JCAR017-BCM-001
Study BCM-003	Study JCAR017-BCM-003
Study FOL-001	Study JCAR017-FOL-001
Submission of application	Submission of application for marketing approval
tiNHL	transformed indolent non-Hodgkin lymphoma