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BLA Clinical Review Memorandum

Application Type	Supplementary BLA
STN	125714.703
CBER Received Date	21 August 2025
PDUFA Goal Date	20 February 2026
Division / Office	DCEH/OCE/MHB
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Robert Sokolic, MD ROBERT A. SOKOLIC -S Digitally signed by ROBERT A. SOKOLIC -S Date: 2026.02.20 10:06:46 -05'00'
Clinical Pharmacology Reviewer	Xing Jing, PhD XING JING -S (Affiliate) Digitally signed by XING JING -S (Affiliate) Date: 2026.02.20 10:23:34 -05'00'
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Associate Director of Labeling	Afsah Amin, MD, MPH, RAC Afsah Amin -S Digitally signed by Afsah Amin -S Date: 2026.02.20 10:11:44 -05'00'
Review Completion Date / Stamped Date	February 20, 2026
Supervisory Concurrence	Upendra Mahat, MD Upendra Mahat -S Digitally signed by Upendra Mahat -S Date: 2026.02.20 10:02:54 -05'00' R. Angelo DeClaro, MD Romeo De Claro -S Digitally signed by Romeo De Claro -S Date: 2026.02.20 11:04:47 -05'00' Bindu George, MD Bindu George -S Digitally signed by Bindu George -S Date: 2026.02.20 11:07:09 -05'00'
Applicant	Juno Therapeutics, Inc. a Bristol-Myers Squibb Company
Established Name	Lisocabtagene maraleucel
(Proposed) Trade Name	Breyanzi
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Formulation(s), including Adjuvants, etc.	Cryopreserved cell suspension for infusion with 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide], 24% Multiple Electrolytes for Injection, Type 1, and 1% of 25% albumin (human). A single dose consists of an equal number of CD4+CART+cells and CD8+ CART+ cells in separate syringes.
Dosage Form(s) and Route(s) of Administration	suspension for intravenous infusion
Dosing Regimen	90 to 110 × 10^6 CAR-positive viable T cells
Indication(s) and Intended Population(s)	Adult patients with relapsed or refractory follicular lymphoma who have received 2 or more prior lines of systemic therapy
Orphan Designated (Yes/No)	Yes

Contents

TABLE OF TABLES

GLOSSARY

AE	adverse event
BLA	biologics license application
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CR	complete response
CRS	cytokine release syndrome
CSR	Clinical study report
FL	Follicular lymphoma
GELF	Groupe d'Etude des Lymphomes Folliculaires
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICAHT	Immune effector cell associated hematotoxicity
IEC-HS	Immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome
iNHL	indolent non-Hodgkin lymphoma
LBCL	Large B-cell lymphoma
LTFU	Long-term follow-up
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal zone lymphoma
NHL	non-Hodgkin lymphoma
OS	Overall survival
PD	pharmacodynamics
PFS	progression-free survival (PFS)
PI	Prescribing information
PK	Pharmacokinetics
PMR	Postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SPM	Second primary malignancy

1. Executive Summary

Lisocabtagene maraleucel (BREYANZI), hereafter referred to as liso-cel, is a CD19-directed genetically modified autologous T cell immunotherapy indicated for treatment of

- relapsed refractory large B-cell lymphoma (including refractory to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy, 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, and relapsed or refractory disease after 2 or more lines of systemic therapy),
- relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor (accelerated approval),
- relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy (accelerated approval),
- relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor, and
- relapsed or refractory marginal zone lymphoma (MZL) who have received at least 2 prior lines of systemic therapy.

The accelerated approval of liso-cel for follicular lymphoma (May 15, 2024) was based on results from Cohorts 1 (4L+ FL) and 2 (3L FL) of Study JCAR017-FOL-001 (TRANSCEND FL), entitled '*A Phase 2, Open-label, Single arm, Multicohort, Multicenter Trial to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (NHL)*' with the initial data cutoff date of January 27, 2023. JCAR017-FOL-001 study included 4 cohorts: Cohort 1 (4L+ FL), Cohort 2 (3L FL), Cohort 3 (2L FL) and Cohort 4 (3L+ MZL). The approval of lisocel for FL included a post marketing requirement (PMR) required according to the regulations for accelerated approval, 21CFR601.41 as below:

"Collect and submit the final report, including datasets from the TRANSCEND FL clinical trial (NCT04245839) to verify and describe the clinical benefit of lisocabtagene maraleucel (BREYANZI) in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). All partial and complete responders should have completed at least 24 months of follow up starting from the initial objective response."

With this efficacy BLA supplement, the Applicant has submitted clinical data from Cohorts 1 and 2 of JCAR017-FOL-001 study with longer follow up for durability of response (i.e. at least 24 months for follow up for all responders since the onset of response). The submission requests to fulfill the

accelerated approval PMR, and provides evidence of effectiveness in support of conversion to a traditional approval for the following indication:

JCAR019-FOL-001 (TRANSCEND FL) is a Phase 2, open-label, single-arm, multicohort, multicenter trial evaluating the efficacy and safety of liso-cel in adult patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma. The study included 114 patients with r/r FL who had received at least 2 prior systemic therapies. The primary endpoint was overall response rate (ORR) per an independent review committee (IRC). Accelerated approval was granted based on efficacy results from 94 patients showing ORR of 95.7% (95% CI: 89.5, 8.8), and a favorable benefit risk assessment. Median duration of response was not reached (95% CI: 18.0, NR) after a median duration of follow up for DOR of 16.8 months (95% CI: 16.3, 17.0).

This supplement contains efficacy and safety data with a new data cutoff date of March 31, 2025.

Efficacy:
A total of 114 3L+ FL patients were Leukapheresed; 103 patients had PET+ measurable disease at baseline, received conforming liso-cel, and have had at least 24 months of follow up (for responders) since the time of first response. The ORR was 91.1% (95% CI: 91.7, 99.4), CRR was 73.8% (05% CI: 64.2, 82.0). Median duration of response was NR (95% CI: 38.51, NR) after a median follow up of 35.38 months (95% CI: 35.06, 35.45). At the time of new data cutoff date, 63 subjects were in ongoing response.

Safety:
The safety data in this submission consists of data from 114 3L+ FL apheresed patients from JCAR019-FOL-001 study with a median of 41.46 months of follow up (range 0.3, 54.0) months. No new subjects were treated during this extended follow up. Twenty-one deaths occurred since the beginning of the study: 8 due to primary malignancy, 4 due to adverse events (1 cardiac event, 3 due to new malignancies), and 5 due to other causes (3 due to COVID-19, 1 due to erythema multiforme and 1 unknown cause). 8 additional deaths occurred since the original BLA submission: 3 due to disease progression, 2 due to new malignancy, 1 due to adverse event, and 2 due to other causes.
No new cases of CRS or ICANS occurred; no new cases of delayed neurotoxicity occurred.
As of the March 31, 2025, data cutoff date, 16 cases of secondary malignancy developed in 11 subjects. This includes additional 12 new SPM events in 8 new subjects: squamous cell carcinoma (2), melanoma and basal cell carcinoma (1), mucoepidermoid carcinoma (1), spindle cell carcinoma (1), colorectal carcinoma (1), MDS (1) and MDS with transformation to AML (1).
In summary, the safety was consistent with safety observed during initial BLA review. New cases of secondary malignancies were observed which is

expected in this relapsed refractory FL population with multiple prior lines of therapy; no new cases of T cell malignancy were reported. No new safety signals were identified during the longer follow up.

Conclusion and Recommendation:

The initial approval of liso-cel for relapsed refractory FL after at least 2 prior lines of systemic therapy was based on high response rate and duration of response, observed in Study JCAR019-FOL-001, an adequate and well-controlled trial.. Given the limited follow-up for duration of response and ultimate clinical benefit, ORR was considered an intermediate clinical endpoint reasonably likely to predict clinical benefit, and therefore an accelerated approval was granted. For verification of clinical benefit, two potential options were considered 1) a randomized trial with a time-to-event endpoint such as PFS or OS or 2) additional follow-up of the current patients in Study FOL-001. The additional follow-up of at least 24 months for duration of response in Study FOL-001 was considered acceptable to verify the clinical benefit of liso-cel in the indicated population based on the following rationale (extracted from BLA Clinical Review and Evaluation BLA 125714/225 available at https://www.fda.gov/media/185920/download?attachment)

- The high magnitude of response with prolonged durability in r/r FL after at least 2 prior lines of systemic therapy is clinically meaningful. Establishment of prolonged durability can be considered clinical benefit in the intended population.
- The safety profile of liso-cel is well established in patients with non-Hodgkin lymphoma, including data from a randomized controlled trial.
- There is no established standard of care for patients with r/r FL receiving 3rd line treatment and beyond, however there are multiple therapeutic interventions that may be considered.
- In patients with r/r FL, outcomes with each successive line of therapy are less, leading to higher mortality after each treatment (see Section 2.1).
- The availability of liso-cel and 2 other CAR T products under accelerated approval for 3rd line treatment of r/r FL may impact the feasibility of accruing and completing a randomized trial.

The data submitted in this supplement continue to demonstrate favorable benefit risk of liso-cel for the indicated FL population. The extended follow up for all responders demonstrate durability of response, and in the context of high CRR and favorable safety profile denotes clinical benefit. The data from JCAR019-FOL-001 continue to demonstrate safety and substantial evidence of effectiveness and therefore supports conversion to

a traditional approval of liso-cel for treatment of adults with relapsed refractory FL after at least 2 prior lines of systemic therapy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

One hundred fourteen subjects with follicular lymphoma were analyzed for this submission. Fifty five percent of the people had had at least three treatments for their lymphoma. For the other forty-five percent, the trial treatment was their third treatment.

The median age of all people analyzed was 62 years old. 63.2% of the people treated in the trial were men and 36.8% were women. 4.4% of people were Hispanic or Latino, 69.3% were not Hispanic or Latino and the remainder did not mention their ethnicity. 55.2% of patients were white, 2.6% were Black or African American and 10.5% were Asian. For 31.6% of people treated, the race was unknown or not collected.

1.2 Patient Experience Data

Table 1 Patient Experience Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	

☐	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin lymphoma (iNHL) in the United States, accounting for approximately 70% of cases of iNHL, and the second most common of all NHL subtypes accounting for about 20% of all NHL cases. The rate of new cases of FL in the US was 2.6 per 100,000 men and women per year based on 2015-2019 cases, age-adjusted, with a death rate of 0.4 per 100,000 per year. The median age at diagnosis of FL in the US in 2021 was 64 years. FL is a heterogeneous disease, clinically characterized by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and other less common sites of extranodal involvement.

Most patients have widespread disease at diagnosis. Histological transformation of FL, most frequently to DLBCL, occurs at a risk of about 2% to 3% per year over at least the first 10 to 15 years. At initial diagnosis, established prognostic factors include age, the number of involved lymph nodal areas, the largest diameter of the largest involved lymph node, Ann Arbor staging, hemoglobin level, bone marrow involvement, and levels of lactate dehydrogenase and β2 microglobulin. These prognostic factors are included in the commonly used FLIPI and FLIPI-2 prognostic indices. FLIPI is highly predictive of treatment outcomes and separates patients into 3 distinct risk groups with 10-year overall survival (OS) rates of 70.7% (low risk; 0-1 risk factor), 50.9% (intermediate risk; 2 risk factors), and 35.5% (high risk; $\geqslant$ 3 risk factors), respectively. In patients with relapsed disease, the types of prior treatments and duration of response to prior treatments may be more important than prognostic scores at the time of diagnosis in predicting the outcomes of subsequent treatments.

Despite the introduction of novel agents, FL remains an incurable malignancy. Although initially indolent and sensitive to a variety of chemotherapeutic agents, FL exhibits a continuous pattern of relapses with decreasing sensitivity to chemoimmunotherapy ultimately leading to a poor outcome. A particularly poor prognostic group are patients that progress within 24 months of initiation of front- line chemoimmunotherapy (POD24), consisting of a combination of an alkylating agent and an anti-CD20 monoclonal antibody with or without other drugs. Tumor burden defined based on specific criteria enumerated by the Groupe d'Etude des Lymphomes Folliculaires (follicular lymphoma study group, GELF) is widely used to define patients in whom immediate therapy is necessary. The development of more efficacious therapies for

patients with R/R FL especially for patients with high-risk disease is an imperative.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Table 2 Therapies with FDA approval for the treatment of relapsed or refractory follicular lymphoma

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint(s)	Trial Design / Results
Treanda® (bendamustine hydrochloride) Alkylating drug	Traditional 31-Oct-2008	Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen	ORR	Single-arm study ORR: 74%; CR: 13%; PR: 57% Median DOR: 9.2 mo
Tazverik® (tazemetostat) Methyltransferase inhibitor	Accelerated (18-Jun-2020)	Treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA- approved test and who have received at least 2 prior systemic therapies; Treatment of adult patients with R/R FL who have no satisfactory alternative treatment options	ORR, DOR	Two single-arm cohorts (E7438-G000-101)[c]: • Cohort 4 - EZH2 mutated FL ORR: 69.0%; CRR: 11.9% Median DOR: 10.9 mo Median of 2 prior lines of therapy • Cohort 5 - EZH2 wild-type FL ORR: 34.0%; CRR: 3.8% Median DOR: 13.0 mo Median of 3 prior lines of therapy
Revlimid® (lenalidomide) Immunomodulatory agent	Traditional (28-May-2019)	In combination with a rituximab product, for the treatment of adult patients with previously treated follicular lymphoma	PFS	AUGMENT RCT: R2 vs rituximab + placebo ORR: 80.3% vs 55.4% CRR: 34.7% vs 19.6%[d] Median DOR: 36.6 vs 15.5 mo (HR = 0.44)[d] Median of 1 prior line of therapy[d] MAGNIFY Single-arm study: R2 ORR: 58.8%; CRR: not reported Median DOR: not reached Median of 2 prior lines of Therapy

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint(s)	Trial Design / Results
Brukinsa (Zanubrutinib) BTK inhibitor	Accelerated (7-MAR-2024)	Relapsed/ refractory FL in combination with obinutuzumab after ⩾2 lines of systemic therapy	ORR	RCT Obinutuzumab ORR 46%, obinutuzumab + zanubrutinib 69%
Rituxan® (rituximab) CD20-directed antibody	Traditional 26-Nov-1997	Relapsed or refractory, low-grade or follicular lymphoma, CD20-positive, B-cell NHL as a single agent	ORR/ DOR	Study 1: ORR: 48%; CRR: 6% Median DOR: 11.2 mo Study 2: ORR: 57%; CRR: 14% Median DOR: 13.4 mo Studies 1 + 3 bulky disease: ORR: 36%; CRR: 3% Median DOR: 6.9 mo
Gazyva® (obinutuzumab) CD20-directed cytolytic antibody	Traditional 26-Feb-2016	In combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab- containing regimen	PFS	RCT: Obin + Ben followed by Obin vs Ben (GADOLIN) Median PFS: not reached vs 13.8 mo (HR = 0.48). ORR: 78.7% vs 74.7% CRR: 15.5% vs 18.7% Median DOR: not reached vs 11.6 mo
Monjuvi (tafasitamab-cxix) Anti-Cd19 monoclonal antibody	Traditional (18-JUN-2025)	Relapsed/ refractory FL in combination with lenalidomide and rituximab	PFS	RCT Lenalidomide + rituximab with or without tafasitamab. Median PFS 22.4 months vs 13.9 months
Zevalin® (ibritumomab tiuxetan) CD20-directed radiotherapeutic antibody	Traditional (19-Feb-2002)	Previously untreated follicular NHL in adult patients who achieve a partial or complete response to first-line chemotherapy	ORR	Study 1: RCT vs rituximab Zevalin ORR: 73%; median DOR 14.2 mo Rituximab ORR: 47%; median DOR 12.1 mo Study 2: single arm ORR: 59%; median DOR 7.7 mo

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint(s)	Trial Design / Results
Epkinly (Epcoritamab-bysp) CD3/CD20 bispecific antibody	Traditional (18-NOV-2025)	Relapsed/ refractory FL after ⩾2 lines of systemic therapy; with lenalidomide and rituximab after 1 line of systemic therapy	ORR; PFS and ORR	Single arm trial, ORR 82%; RCT Lenalidomide and Rituxan with or without epcoritamab median PFS NR vs. 112 months, ORR 89% vs 74%
Lunsumio® (mosunetuzumab-axgb) Bispecific CD20-directed CD3 T-cell engager	Accelerated (22-Dec-2022)	Treatment of adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy	ORR	Single-arm study (GO29781) ORR = 80.0%; CRR = 60.0% Median DOR = 22.8 mo Median of 3 prior lines of therapy
Kymriah® (tisagenlecleucel) CD19-directed genetically modified autologous T-cell immunotherapy	Accelerated (27-May-2022)	Treatment of adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy	ORR, DOR	Single-arm study (ELARA) ORR = 86.0%; CRR = 68.0% Median DOR = not reached Median of 4 prior lines of therapy
Yescarta® (axicabtagene ciloleucel) CD19-directed genetically modified autologous T-cell immunotherapy	Accelerated (05-Mar-2021)	Treatment of adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy	ORR	Single-arm study ORR: 91%; CRR: 60% Median DOR: not estimable. Median of 3 prior lines of therapy

2.3 Safety and Efficacy of Pharmacologically Related Products

Liso-cel is an autologous CAR-T cell directed product. Other CAR-T cell products indicated for the treatment of relapsed or refractory follicular lymphoma are Axicabtagene ciloleucel (Axi-cel, Yescarta, accelerated approval) and Tisagenlecleucel (tisa-cel, Kymriah, accelerated approval). Primary safety concerns with axi-cel and tisa-cel are typical of the concerns of the CAR-T cell class: Immune-mediated adverse events and second primary malignancies. Immune-mediated adverse events include cytokine release syndrome (CRS), Immune effector cell-associated neurological syndrome (ICANS), Immune effector cell associated hemophagocytosis-like syndrome (IEC-HS), and immune effector cell-associated hematotoxicity (ICAHT), in addition to allergic reactions and infusion reactions. Allergic and infusion reactions are common to all cellular products, are well understood and have effective therapies. The acute toxicities such as CRS, ICANS, IEC-HS, ICAHT can have variable severity, ranging from mild to life-threatening critical illness events. While there are accepted treatment algorithms for all of these syndromes, optimal treatment of these syndromes is not well understood, and each syndrome can lead to death of a treated patient.

Secondary malignancies, resulting from genotoxicity of the retroviral vectors used to manufacture CAR T cells and potentially other mechanisms, have been seen reported with both tisa-cel and axi-cel (as well as with liso-cel).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Liso-cel is approved for various hematological malignancies as shown in **Error! Reference source not found.**.

Table 3. Efficacy Results for Liso-Cel in Different Indications

Approved Indications	**Approval (Date)**	**Basis for Approval (Trial design, sample size, efficacy endpoint, results)**	**Confirmatory Trial in Case of Accelerated Approval**
Adults with relapsed or refractory LBCL after 2 or more lines of systemic therapy	Traditional (February 5, 2021)	TRANSCEND, a single-arm trial, N=192, CRR, 54% (95% CI: 47, 61)	NA
Adults with LBCL that is • refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy; or • refractory to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation due to comorbidities or age	Traditional (June 24, 2022)	• TRANSFORM, an RCT, N= 92 in Breyanzi arm vs 92 in SOC arm, median EFS of 10.1 months (95% CI: 6.1, NR) in Breyanzi vs 2.3 months (95% CI: 2.2, 4.3) in SOC arm with HR of 0.34 (95% CI: 0.22, 0.52) • Pilot single arm, N=61, CRR, 54% (95% CI: 41, 67)	NA
Adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor	Accelerated (March 14, 2024)	TRANSCEND-CLL, a single-arm trial, N=65, ORR, 45% (95% CI: 32, 58)	A single-arm trial of 50 pts with CLL/SLL with at least 15 months of DOR follow up
Adults with relapsed or refractory FL after two or more lines of systemic therapy	Accelerated (May 15, 2024)	TRANSCEND-FL, a single- arm trial, N=94, ORR, 96% (95% CI: 90, 99)	At least 24 months DOR follow up for TRANSCEND-FL patients
Adults with relapsed or refractory mantle cell lymphoma who have received at least 2 prior lines of systemic therapy, including a	Traditional (May 30, 2024)	TRANSCEND-MCL, a single-arm trial, N=68, ORR, 85% (95% CI: 75, 93)	NA

Approved Indications	Approval (Date)	Basis for Approval (Trial design, sample size, efficacy endpoint, results)	Confirmatory Trial in Case of Accelerated Approval
Bruton tyrosine kinase (BTK) inhibitor			

Source: Breyanzi USPI

Key toxicities of liso-cel are similar in different approval indications, and include CRS, ICANS/neurotoxicity, IEC-HS and risk of secondary malignancies.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Liso-cel's original approval for follicular lymphoma included a requirement to collect additional data on the TRANSCEND-FL trial to verify and describe the clinical benefit of lisocabtagene maraleucel (BREYANZI) in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). All partial and complete responders were to have completed at least 24 months of follow up starting from the initial objective response.
The current supplement includes data submitted in fulfillment of this post-marketing requirement. No further regulatory interactions relevant to the follicular lymphoma approval were had since the original approval for that indication. A summary of prior regulatory interactions presented for the previous review is reproduced below:

Table 4 Applicant's Summary of Major IND Regulatory Activities Relating to FL Development

Date	Activity and Purpose	FDA Feedback
29-May-2015	IND 016506 Submission	IND 016506 Study may proceed received on 26-Jun- 2015
07-Sep-2017	FDA granted ODD	Designation: Treatment of FL (US Orphan Designation Number 17-6005)
05-Dec-2019	Submission of original protocol JCAR017-FOL-001 to IND 016506 (SN 0585)	Not applicable
13-Jul-2021	Type B End of Phase 2 Meeting IND 016506, CRMTS# 13362	• GELF Criteria: FDA initially questioned the use of high-tumor burden patients as a prognostic factor but did not have strong objections with their inclusion in 2L. Need to ensure that the study as designed/powered will result in an interpretable study and that the primary analysis is not driven solely by POD24.

Date	Activity and Purpose	FDA Feedback
	To obtain the Agency's guidance regarding the proposed global Phase 3 study concept in the expanded indication of R/R FL (Study CA082-011)	• POD24 Definition: Define POD24 as relapse or progression within 24 months of initiation of first-line chemoimmunotherapy. • Comparator Arm: Add R2 as an option for 2L patients and consider R-CVP and obinutuzumab (instead of rituximab) to the standard of care arm (both 2L and 3L). For subjects in the US, only an FDA approved biosimilar would be acceptable; for non-US sites data on the source of the biosimilar needs to be captured. • Disease Assessments: While BMB will be done on all patients at screening, FDA agreed that BMB to confirm CR would only be required in those patients that had positive BM at screening or where baseline BMB was not available/uninterpretable. • FDA strongly discouraged an interim analysis for efficacy at less than 75% information fraction. If conducted, the interim analysis should be ≥ 75% information fraction level for the primary efficacy outcome and accrual must be completed before the interim analysis is performed. • A non-conforming product futility analysis should be included. • If a statistical claim of superiority for HRQoL is sought, the HRQoL hypothesis should be tested within the main statistical hierarchy of the clinical trial with a pre-specified analysis.
22-Feb-2022	Type C Meeting IND 016506, CRMTS#13766 To review the most recent data from Study FOL-001 and to obtain FDA feedback on the: • Planned sample size and follow-up needed for registration in R/R FL and R/R MZL • Primary endpoints and definition from Study FOL-001 Key aspects of the format and content of the planned sBLA dossier for R/R FL and R/R MZL	• For any PET-based response assessments in subjects with FL or MZL, who achieve a metabolic CR, a negative post-treatment BMB is necessary to permit the CR designation in subjects having a positive, indeterminate, or unknown BMB status at study entry; otherwise, the response will be considered a PR for the main efficacy analyses. • FDA further iterated that, per the 2014 Lugano criteria, there are insufficient data in histologies other than DLBCL and Hodgkin lymphoma to support PET alone for disease assessment in the bone marrow. Thus, subjects deemed to have a CR to therapy by imaging criteria must have a bone marrow examination documenting absence of disease to be considered a complete responder if baseline bone marrow examination was positive, indeterminate, or unknown for lymphoma involvement; without this confirmatory BMB, response would be downgraded to PR. The Agency's primary efficacy analysis and the regulatory decision will follow the Lugano criteria. • To support the efficacy and benefit/risk determination, the Agency strongly advised that all responding subjects have a minimum of 12-month follow-up for DOR, measured from the date of first objective response to the date of last adequate (radiographic) disease assessment (not to the data cut-off date). The adequacy of follow-up will be a review consideration. • Sample Sizes: Although the proposed number of ~90 FL subjects treated with liso-cel may be sufficient and sample size calculations can be verified, it is unlikely that 40 MZL subjects treated with liso-cel would be adequate to support a MZL indication. FDA strongly advised increasing the number of MZL subjects treated in Study FOL-001 to inform both efficacy and safety outcomes. Furthermore, there should be an adequate representation of the various MZL subtypes (i.e., nodal, extranodal, and splenic) in the study population.

Date	Activity and Purpose	FDA Feedback
		• Efficacy: FDA requested to have clinical efficacy narratives in a paragraph format which describe the radiographic findings, IRC assessment, the clinical decision, and the rationale for the overall disease determination. The FDA clarified that the efficacy narratives should be submitted for cases of investigator-assessed clinical progressive disease that were not assessed as progressive on IRC assessment and should contain sufficient detail to permit an adjudication of disease status. • Safety: FDA did not agree with the Sponsor's plan to not include an ISS in the sBLA. FDA requested inclusion of liso-cel studies/disease cohorts in a side-by-side comparison table of safety with the goal of facilitating the detection of clinically meaningful differences in safety between Study FOL-001 and other relevant liso-cel studies. FDA also requested that the summary should include an assessment, discussion of the relevant safety differences between the studies and justification for the integration of proposed studies. • Confirmatory Study: Should accelerated approval be granted, continued approval would likely be contingent upon verification of clinical benefit in a clinical trial(s). The confirmatory trial should be ongoing at the time of sBLA submission.

Source: FDA review memo for initial FL application

2.6 Other Relevant Background Information

This supplemental application is meant to convert accelerated approval for follicular lymphoma to traditional approval. It consists only of additional data on subjects previously enrolled on trial JCAR019-FOL-001 (TRANSCEND FL, hereafter referred to as Study FOL-001).out to 24 months.

OCE MORE TL Comment:
The OCE MORE TL agrees that the Applicant has submitted the data as specified in the PMR that was issued with the accelerated approval of liso-cel for patients with R/R FL after at least 2 prior therapies. In general, for confirmation of clinical benefit for accelerated approval based on durable responses in a single arm trial in follicular lymphoma, a randomized trial evaluating a time to event endpoint such as OS or PFS is required. Based on prior discussions with Applicant occurring in May of 2024, the rationale for requiring additional longer follow up for patients evaluated in the single arm study supporting accelerated approval for liso-cel in patients with R/R FL after at least two prior therapies was based, in part, on the following:

- *The high magnitude of response with prolonged durability in R/R FL after at least 2 prior lines of systemic therapy is clinically meaningful. Establishment of prolonged durability after a single administration of liso-cel can be considered clinical benefit in the intended population.*

With a median follow up for DOR of 35.4 months (95% CI 35.1, 35.5), the data included in this submission demonstrates durable responses (ORR of 97%, CRR of 74%, with a median duration of response not reached (95% CI 38.5 months NR) after a single dose of liso-cel which confirms the clinical benefit of liso-cel in patients with R/R FL after at least 2 prior therapies.

Reviewer Team's comment: *The conversion from accelerated approval to the traditional or regular approval is based on the extended duration of follow up data on the intermediate clinical benefit endpoint of ORR. The follow up period for duration of ORR at the time of accelerated approval ranged from 1.9 months to 23.1+ months (ongoing response) to 1.9 months to 47.9+ months with ongoing responses. The additional data obtained for the duration of overall response, complete response and partial response provide satisfactory assurance of clinical benefit sufficient to provide evidence of effectiveness to support traditional approval and is consistent with the FDA 2024 Draft Guidance "Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry".*

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant provided adequate documentation that the research study conducted was in accordance with Good Clinical Practices. No additional inspections were performed for this review.

3.3 Financial Disclosures

Table 5 Financial Disclosure

Covered clinical study (JCAR017-FOL-001; NCT04245839):
Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant)
Total number of investigators identified: 829
Number of investigators who are sponsor employees (including both full-time and part-time employees): 1
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5

Covered clinical study (JCAR017-FOL-001; NCT04245839):
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? X Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? X Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 5 Is an attachment provided with the reason? X Yes ☐ No (Request explanation from applicant)

Source: Applicant financial disclosure, module 1.3.4

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Not applicable. There were no changes to CMC considerations since the previous data review.

4.2 Assay Validation

Not applicable

4.3 Nonclinical Pharmacology/Toxicology

Not applicable. No new non-clinical studies were presented in this application.

4.4 Clinical Pharmacology

As described in Section 1, the sBLA approval for the FL population included a PMR that required all partial and complete responders to have completed at least 24 months of follow up starting from the initial objective response. To fulfill this PMR, in this current application, the Applicant updated efficacy analysis by including an additional 9 subjects(updated n=103) who had at least 24 months of follow up from the date of first response. As a result, the pharmacokinetics of LISO-CEL was updated to reflect the addition of these 9 participants.

4.4.1 Mechanism of Action

No change from previous approval.

4.4.2 Human Pharmacodynamics (PD)

No change from previous approval.

4.4.3 Human Pharmacokinetics (PK)

The median time of maximal expansion in peripheral blood occurred 10 days after infusion. Median Cmax and AUC0-28d are 33604 copies/µg and 253400 day*copies/µg, respectively. Lisocel was present in peripheral blood for an estimated median of 12.0 months (range: 0.3+ to 48.1 months).

4.5 Statistical

There were no significant safety or efficacy issues related to the statistical review.

4.6 Pharmacovigilance

Liso-cel was originally approved with a REMS due to risk of serious and potentially life- threatening complications of CRS and neurotoxicities. REMS included ETASU and required that hospitals and associated clinics dispensing liso-cel be certified and have on-site, immediate access to tocilizumab and that health care providers involved in the prescribing, dispensing, or administering of the product be trained to recognize and manage CRS and neurotoxicity.

The Office of Biostatistics and Pharmacovigilance initial review memo can be referred to for details.

On June 27, 2025, FDA eliminated the Risk Evaluation and Mitigation Strategies (REMS) for currently approved BCMA- and CD19-directed autologous chimeric antigen receptor CAR T cell immunotherapies, including lisocel. FDA's decision to remove REMS was based on the determination that safe and effective use of the CAR T cell products for the indicated population can be assured without a REMS, and that adverse event reporting for CRS and ICANS has remained stable. Based on the safety data of lisocel in FL population with extended follow up, no new safety information, including no new cases of CRS or ICANS were identified necessitating REMS, and therefore no new REMS is required for this approval.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review included review of patient label data from JCAR017-FOL-001 study. The focus of this review was the comprehensive time point to time point efficacy

review for 9 additional subjects with FL, and review/confirmation of durability of response for all patients with FL. The review also included safety review with extended follow up.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Data from a single trial were reviewed, trial JCAR017-FOL-001; NCT04245839; Documents reviewed included the cover letter and priority review request, the clinical overview in module 2, Addendum 2 to the CSR, including efficacy and safety narratives, and the following datasets: ADAE, ADAEME, ADBM, ADCMS, ADDX, ADPE, ADRS, ADSL, ADTTE, CE, PE, SUPPRS, DS and TR. Individual CRFS were reviewed as needed

The initial review of the FOL-001 study, used for granting accelerated approval was also reviewed.

Table 6 Table of Studies/Clinical Trials

Study	Phase	Test Product	Duration of treatment	N	Population	Follow-up
JCAR017-FOL-001; NCT04245839	2	Liso-cel; 100×10^6 CAR+ T cells; intravenous	Single dose	107	Adults with R/R FL after at least two lines of treatment	24 months

6. Discussion of Individual Studies/Clinical Trials

6.1.2 Design Overview

JCAR017-FOL-001 Study:

Study FOL-001 is a Phase 2, open-label, single-arm, multicohort, multicenter trial to evaluate the efficacy and safety of liso-cel in adult subjects with R/R iNHL, including FL and MZL. The study was conducted at 30 sites in 10 countries (Austria, Canada, France, Germany, Italy, Japan, Spain, Sweden, United Kingdom, and US) for FL treated subjects.

Table 7 Trial FOL-001 Design

Title	A Phase 2, Open-label, Single-arm, Multicohort, Multicenter Trial to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects with Relapsed or Refractory iNHL

Objectives/ Endpoints	Primary objective/endpoint: to evaluate the efficacy of liso-cel in subjects with R/R FL, and MZL. Primary endpoint: ORR by IRC as assessed by CT (for MZL) or PET-CT (for FL) using a modified Lugano Classification.[i] Secondary objectives/endpoints: evaluation of other measures of efficacy, evaluation of the safety of liso-cel (type, frequency, and severity of AEs and laboratory abnormalities), characterization of the PK profile of liso-cel, and evaluation of HRQoL using preselected primary domains of interest in the EORTC QLQ-C30 and FACT-LymS. Secondary efficacy endpoints: CR rate by IRC, DOR if BOR is CR, DOR, PFS, and OS.
Study Design	Phase 2, open-label, single-arm, multicohort, multicenter study to evaluate the efficacy and safety of liso-cel in adult subjects with R/R FL and MZL. The study is divided into 3 periods: Pretreatment (screening assessments, leukapheresis, and pretreatment evaluation), Treatment (starts with the administration of LDC and continues through liso-cel administration at Day 1 with follow-up through Day 29), Posttreatment (follow-up assessments for disease status, efficacy, and safety for 5 years). Upon study completion, or early discontinuation, subjects were asked to consent to participate in a LTFU study for up to 15 years after the dose of liso-cel. Approximately 213 subjects were expected to be enrolled worldwide with the aim to treat approximately 170 subjects across 4 cohorts, as follows: • Cohort 1 (4L+ R/R FL): approximately 50 treated subjects • Cohort 2 (3L R/R FL): approximately 40 treated subjects • Cohort 3 (2L R/R FL): approximately 20 treated subjects • Cohort 4 (3L+ R/R MZL): approximately 60 treated subjects. Following confirmation of study eligibility, all subjects undergo leukapheresis to enable liso-cel product generation. If necessary, optional anticancer treatment (bridging therapy) was allowed for disease control while liso-cel was being manufactured but must be completed at least 7 days (or 3 half-lives for oral chemotherapeutic agents) prior to the start of LDC. If optional anticancer treatment was necessary during this time, the pretreatment PET and CT/MRI assessments and other select pretreatment study procedures must have been performed after the optional anticancer treatment has been completed. In MZL cohort, the subject must have continued to have measurable disease by CT and meet eligibility criteria. Treatment Period began with the administration of LDC followed by liso-cel infusion at a dose of 100 × 10^6 CAR+ T cells on Day 1.
Study Population	R/R FL (Grade 1, 2, or 3a) or MZL, histologically confirmed within 6 months of screening.
Study Treatments	LDC with IV fludarabine (30 mg/m²/day for 3 days) plus IV cyclophosphamide (300 mg/m²/day for 3 days) concurrently followed 2 to 7 days later by liso-cel infusion at a dose of 100 × 10^6 CAR+ T cells.
Efficacy Assessments	Efficacy was assessed by radiographic tumor evaluation by diagnostic quality CT/MRI scans (chest, neck, abdomen, and pelvis) and/or PET scans according to a modified Lugano Classification,[i] reviewed by an IRC. Upon documentation of progressive disease or administration of additional anti-lymphoma treatment, response assessments were no longer required (except for HSCT). Efficacy assessments were/will be performed at screening, prior to LDC, on Day 29 of treatment period, and during follow-up period (Days 90, 180, 270, 365, 545, 730 (Month 24), and Months 36, 48, and 60 (end of study) after the final liso-cel administration).
Safety Assessments	Safety evaluations include AE/SAE collection, concomitant medication and procedure assessment, laboratory evaluations, physical examinations, and vital sign assessment. The study data were regularly reviewed by an independent data safety monitoring board.

6.1.3 Population

Inclusion criteria

- Relapsed or refractory FL (Grade 1, 2, or 3a) with at least one PET-positive lesion and at least one measurable nodal or extranodal lesion

- Previous treatment with at least 2 prior lines of systemic therapy, including a combination anti-CD20/alkylator regimen.
- Subjects who have received previous CD19-targeted therapy must have had CD19-positive lymphoma
- ⩾ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ and marrow function as defined by protocol.

Exclusion Criteria

- Composite DLBCL and FL
- Transformed FL
- World Health Organization (WHO) sub-classification of duodenal-type FL
- Central nervous system (CNS)-only involvement by malignancy
- Prior CAR T-cell or other genetically modified cell therapy
- Active autoimmune disease or GvHD requiring immunosuppressive therapy

6.1.4 Study Treatments or Agents Mandated by the Protocol

Leukapheresis
Lymphodepleting chemotherapy
Fludarabine (30 mg/m2/day for 3 days)
Cyclophosphamide IV (300 mg/m2/day for 3 days)
Both drugs given concurrently
Investigational agent
Liso-cel 100e6 CAR+ T Cells as a single infusion

6.1.6 Sites and Centers

See 6.1.2

6.1.7 Surveillance/Monitoring

Participants were monitored for 24 months.

Baseline evaluation included: Physical examination, neurologic exam, vital signs, EKG, MUGA or echocardiogram, HBV, HCV and HIV serology, serum pregnancy test, creatinine clearance, CBC, coagulation parameters (PT, aPTT, INR, fibrinogen, and D-dimer) chemistries, CRP, ferritin, immunoglobulins, and SARS-CoV 2 serology.

Lymphodepletion was carried out days -9 to -4. While most participants were hospitalized, hospitalization was not mandated. Study visits during the treatment period were on days 1,4,8,11,15,22 and 29. Liso-cel treatment was on day 1. Thereafter participants were seen at months 2,3,6,9,12,18 and 24. After 24 months patients enrolled on a companion long-term follow-up study.

Physical exam was carried out weekly to day 29, and then at every visit.
MMSE was performed days 1 and 4, weekly to day 29 and at day 90.
Neurologic exam was performed at every visit through day 29 and at day 90.
Vital signs and pulse oximetry were performed at every visit through day 29.
CSF examination was performed as clinically indicated.
CBC was checked at every visit.
Coagulation, chemistry, ferritin and CRP were checked at every visit to day 29
Immunoglobulins were tested at every visit starting from day 15.

An independent DSMB was used.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Overall Response Rate, as assessed by PET-CT using The Lugano criteria. Response was adjudicated by an independent review committee.

Secondary endpoints: Complete Response Rate as assessed by PET-CT using Lugano criteria; Duration of Response if Best Overall Response is CR; Duration of Response; Progression-Free Survival as assessed by PET-CT using Lugano criteria; Overall Survival; Safety as assessed by type, frequency, and severity of adverse events and laboratory abnormalities;, Pharmacokinetics; and HRQoL by EORTC QLQ-C30 selected subscales and by FACT-LymS

Exploratory endpoints: Immunogenicity; Flow cytometry for immune subsets; gene expression profiling; cfDNA/MRD; Peripheral B cell aplasia; Tumor Biomarkers; Health-Related Quality of Life by remaining EORTC-QLQ-30 subscales; Health Utility and Global Health Assessment by EQ-5D-5L health utility and visual analog scale scores; Hospital Resource Utilization by ICU days, inpatient days and outpatient visits; and COVID-19 serology status

Review team's comment*: These were exploratory endpoints and were not reviewed for regulatory decision making. Health related quality of data were submitted during initial BLA submission for FL indication. Given the single arm design of the study with no concurrent control arm, these data were considered exploratory and were not used to inform regulatory decision making.*

All chosen endpoints are accepted standards in the field ad were used appropriately. Endpoints were not modified after completion of the protocol.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary endpoint (ORR) and the CRR and DOR secondary endpoint analyses were confirmed.

6.1.10 Study Population and Disposition

6.1.10.1 Disposition

A total of 139 subjects with FL were enrolled in study JCAR-FOL-001, including 114 FL subjects with at least 2 prior lines of therapy (i.e. 3L+ FL).

Of the 114 3L+ leukapheresed subjects, 107 (93.9%) subjects were infused with a dose of conforming lisocel. See Table 8

Table 8. Disposition of subjects: JCAR017-FOL-001 study

Disposition	**3L+ FL (N)**
All Leukapheresed 3L+ FL	114
Leukaphersed and received conforming lisocel	107
Leukaphersed but did not receive conforming lisocel	7
Received non conforming liso-cel	4
Adverse reaction	1
Failure to meet exclusion/inclusion criteria	1
Not reported	1
Received conforming liso-cel but did not have baseline PET-CT after Bridging	4
Source: ADSL data, Study JCAR017-FOL-001; and CSR	

As of the 31-Mar-2025 data cutoff, 106 (99.1%) subjects had completed the treatment period (Days 1 to 29) with 78 (72.9%) subjects that continued to and were ongoing in the Posttreatment Period (Day 30 to Month 60), 27 (25.2%) had discontinued, and 3 (2.8%) subjects transferred to the LTFU study

6.1.10.2 Demographics

Demographics are presented in the table below:

Table 9 Demographics of Efficacy Set

Parameter	4L+ FL (N=55)	3L FL (N=48)	3L+ FL (N=103)
AGE (YEARS)			
N	55	48	103
Mean	62.8	59.7	61.4
StdDev	9.91	10.45	10.24
Median	64	60	62
Q1, Q3	56.0, 70.0	53.5, 67.0	55.0, 69.0
Min, Max	23, 80	27, 78	23, 80
AGE GROUP (YEARS) - N (%)			
< 65	31 (56.4)	31 (64.6)	62 (60.2)
≥ 65 - < 75	18 (32.7)	14 (29.2)	32 (31.1)
≥ 75	6 (10.9)	3 (6.3)	9 (8.7)
SEX - N (%)			
Female	23 (41.8)	17 (35.4)	40 (38.8)
Male	32 (58.2)	31 (64.6)	63 (61.2)
ETHNICITY - N (%)			
Hispanic or Latino	4 (7.3)	1 (2.1)	5 (4.9)
Not Hispanic or Latino	37 (67.3)	35 (72.9)	72 (69.9)
Not Reported	14 (25.5)	12 (25.0)	26 (25.2)
Unknown	0	0	0
PRIMARY RACE - N (%)			
American Indian or Alaska Native	0	0	0
Asian	6 (10.9)	3 (6.3)	9 (8.7)
Black or African American	3 (5.5)	0	3 (2.9)
Native Hawaiian or Other Pacific Islander	0	0	0
White	30 (54.5)	29 (60.4)	59 (57.3)
Not Collected or Unknown	16 (29.1)	16 (33.3)	32 (31.1)
REGION - N (%)			
Europe	24 (43.6)	34 (70.8)	58 (56.3)
Japan	5 (9.1)	3 (6.3)	8 (7.8)
North America	26 (47.3)	11 (22.9)	37 (35.9)

L = number of prior lines of therapy
Source: FDA analysis of ADSL data from JCAR017-FOL-001 study; and CSR Table 14.1.3.1.1

6.1.10.3 Efficacy Analyses

During the review of the initial BLA of lisocel for FL (BL 125714/225), 103 subjects had two or more prior lines of therapy (3L+ FL), and had received conforming lisocel. Ninety-four out of these 103 subjects in 3L+FL were used for primary analysis of efficacy. These 94 FL subjects had histologically confirmed FL (Grade 1, 2 or 3a), evidence of PET-positive measurable disease per Lugano criteria, received one dose of conforming lisocel and had a minimum of 9 months of follow up for DOR. Seven subjects were excluded from FDA's primary efficacy evaluable population since they did not have a minimum of 9 months of DOR follow up, and 2 subjects were excluded due to lack of IRC confirmed measurable disease at baseline.

In this submission with extended follow up, all responding subjects (CR or PR) have completed a minimum of 24 months of follow up, and the imaging for 2 subjects were re-evaluated by IRC confirming presence of measurable disease at baseline. Therefore, the primary efficacy evaluable population includes a total of 103 subjects with histologically confirmed FL (Grade 1, 2 or 3a), evidence of PET-positive measurable disease per Lugano criteria, received one dose of conforming lisocel and had a minimum of 24 months of follow up for DOR. Additionally, sensitivity efficacy analysis was performed in all leukaphersed 3L+ FL population (N=-114). This analysis plan is consistent with the statistical analysis plan as outlined in JCAR017-FOL-001 protocol and SAP.

The data cutoff was 31 March 2025.

6.1.10.4 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the Overall Response Rate, as assessed by PET-CT using Lugano criteria, including required bone marrow biopsies for participants previously known to have marrow involvement, or whose marrow status was unknown at baseline. Responses were assessed by an independent review committee. One hundred of the 103 participants responded for an ORR of 97.1% (95% CI 9.7 to 99.4%). The efficacy data is consistent with the ORR reported at the previous analysis (95.7%)

Table 10 Efficacy Outcomes Trial FOL-001

	Primary efficacy population, per FDA algorithm* (N=103)	**All Leukapheresed Patients (N=114)**
Overall Response Rate*, n (%)	100 (97.1)	105 (92.1)
[95% CI]	[91.7, 99.4]	[85.5, 96.3]
Complete Response, n (%)	76 (73.8)	78 (68.4)
[95% CI]	[64.2, 82.0]	[59.1, 76.8)
Partial Response, n (%)	24 (23.3)	27(23.7)
[95% CI]	[15.5, 32.7]	(16.2, 32.6)
Source: FDA's primary review of ADRS, ADTTEIRC, ADTR/TU, ADBM datasets, clinical study report and FDA statistical reviewer's memo **Response per FDA Algorithm represents the IRC assessed response per Lugano CI: Confidence interval		

6.1.10.5 Analyses of Secondary Endpoints

Secondary endpoints reviewed for this analysis were Complete Response Rate, Partial Response Rate and Duration of Response.

See CRR and PRR in **Error! Reference source not found.**

After a median follow up for DOR of 35.38 months (95% CI: 35.06 to 35.45; minimum 1.9, max 47.9 months), the median DOR was not reached (95% CI: 38.51, NR). The duration of response is shown in Figure 1 and Table 11.

Figure 1. KM Plot of DOR in the Efficacy Analysis Set (Source: FDA statistical reviewer memo)

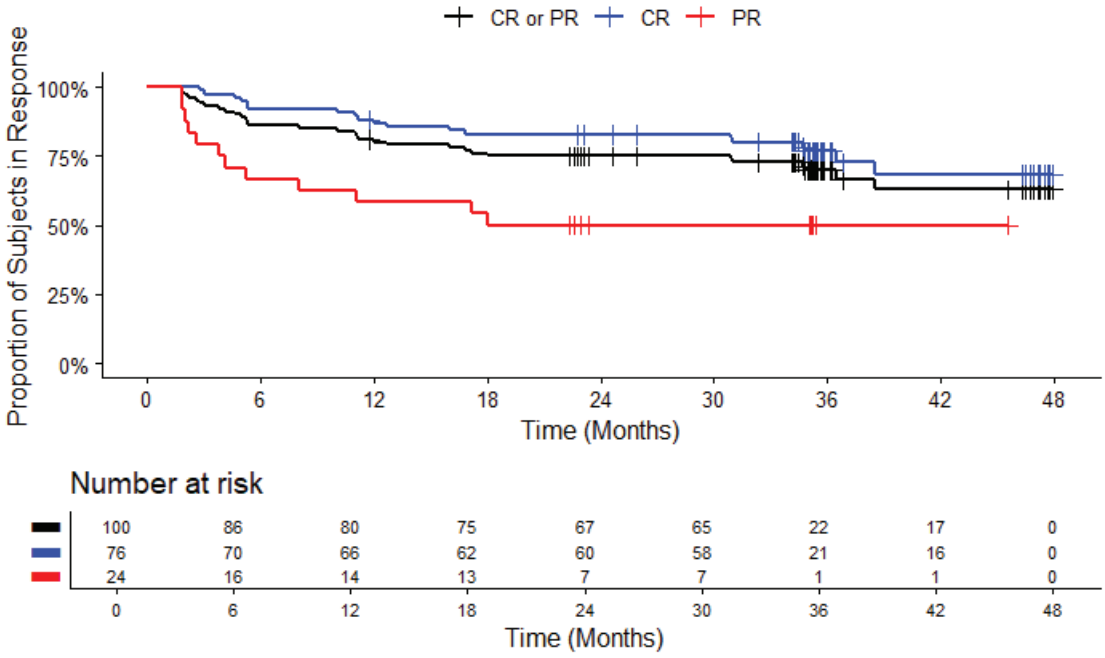

Table 11. Duration of Responses in Patients with Relapsed or Refractory FL

	BREYANZI Treated[b] N = 103
Number of Responders	**100**
DOR (months)	
Median [95% CI][c]	NR (38.51, NR)
Range	1.9, 47.9+
Rate at 12 months, (%) [95% CI][d]	81.0 (71.8, 87.4)
Rate at 24 months, (%) [95% CI][d]	74.9 (65.2, 82.3)
DOR if best response is CR (months)	**N=76**
Median [95% CI][c]	NR [NR, NR]
Range	2.8, 47.9+
Rate at 12 months, (%) [95% CI][d]	88.2 (78.5, 93.7)
Rate at 24 months, (%) [95% CI][d]	82.8 (72.2, 89.6)
DOR if best response is PR (months)	**N=24**
Median [95% CI][c]	NR [4.17, NR]
Range	1.9, 45.5+
Rate at 12 months, (%) [95% CI][d]	58.3 (36.4, 75.0)

Rate at 24 months, (%) [95% CI][d]	50.0 (29.1, 67.8)

Review Team's comment*: The observation of sustained response in both complete and partial responders coupled with the very high ORR supports that durable ORR inclusive of both duration of CR and PR, represents clinical benefit in 3L+ FL patients, and therefore supports a traditional approval of liso-cel for this patient population.*

6.1.10.6 Subpopulation Analyses

No such populations analyzed

6.1.10.7 Exploratory and Post Hoc Analyses

Not applicable

6.1.11 Safety Analyses

6.1.11.1 Methods

The safety population included 114 participants who enrolled after 2 or more lines of therapy and underwent apheresis. No new subjects were treated with lisocel since previous data cutoff date, and no subject received repeat treatment with lisocel. The safety review focused on new safety events.

At the time of the interim CSR data cutoff, all 3L+ FL liso-cel treated subjects from Study FOL-001 had completed the treatment-emergent period, with one subject discontinued the study during that period.
At the new data cutoff date of March 31, 2025, the median follow up duration is 41.46 months (range: 0.3, 54.0 months). The overall safety profile is consistent with the safety profile observed in previous data cutoff date of January 27, 2023.

6.1.11.2 Overview of Adverse Events

The safety review was based on 107 3L+ FL subjects who were treated with conforming lisocel. All subjects had completed treatment emergent period (i.e. 90 days following lisocel infusion) during review of initial BLA for FL with data cutoff date of January 27, 2023.

Deaths

There were 8 new deaths: 3 due to disease progression, 2 due to new malignancy or complications from new malignancy, 1 due to adverse event, and 2 due to other causes.

- **Subject** (b) (6) was an 80-year-old Black or African American man. The participant's best overall response was a partial response, but he suffered progressive disease on day 269. He received further anti-lymphoma therapy, but ultimately goals of care were reoriented towards comfort, he was admitted to hospice, and he died on day 1286 of unknown cause.

- **Subject** (b) (6) was a 68year-old white man. He was treated with non-conforming lisocel. The subject initially attained a complete response to liso-cel infusion. He suffered progressive disease and was reported to have died from lymphoma on day 1124.

- **Subject** (b) (6) was a 53-year-old white man. His post lisocel infusion course was complicated by grade 1 CRS, grade 1 tremor, prolonged cytopenias, COVID-19 pneumonia, and hypogammaglobulinemia. He attained a complete response to liso-cel infusion. On day 662 (b) (6)), he developed a grade 4 myelodysplastic syndrome with a TP53 mutation. This eventually transformed to acute myeloid leukemia by day 838. The participant's further clinical course was complicated by Covid-19 infection, norovirus gastroenteritis and septic shock leading to death on day 971.

- **Subject** (b) (6) was a 49-year-old white man. He was infused with liso-cel on (b) (6) . His post-infusion course was complicated by grade 1 CRS and grade 3 covid pneumonia. He attained a complete response. About 3 years after his infusion, the participant developed back pain. This was found to be caused by an extradural mass lesion at the level of the lumbar spine. This lesion was found to be a spindle cell sarcoma on day 1121. The participant was treated with gemcitabine and docetaxel. The participant developed neutropenia and died of septic shock on day 1200 (b) (6)

- **Participant** (b) (6) was a 71-year-old man whose race and ethnicity were not reported. His post-infusion course was complicated by prolonged cytopenias. He suffered progression of disease as assessed by the investigator on day 27 and was given additional anti-lymphoma treatment. On day 886 (b) (6)) the patient died of progressive disease.

- **Participant** (b) (6) was a 55-year-old white man whose post infusion course was complicated by grade 2 CRS and prolonged cytopenias beyond day 29. He attained a complete response to liso-cel infusion. On day 883 the participant developed a grade 4 myelodysplastic syndrome. This was attributed to previous chemotherapy including high dose therapy with autologous hematopoietic cell transplantation. The subject was ultimately treated with allogeneic hematopoietic cell transplantation, but died with persistent MDS on day 1079 (b) (6))

- **Participant** (b) (6) was a 70-year-old white man. His post-infusion course was complicated by prolonged cytopenias. He attained a complete response to liso-cel infusion but developed progressive disease on day 184 (b) (6)). He eventually died of COVID-19 pneumonia.

- **Participant** (b) (6) was a 65-year-old Asian man. He was treated with non-conforming product, to which he attained a complete response. He died on day 100 ((b) (6)) from COVID-19 infection.

Reviewer comment: None of the above deaths were considered to be related to liso-cel infusion. Labelling changes based on these deaths were not suggested

6.1.11.3 Nonfatal Serious Adverse Events

Not applicable.

6.1.11.4 Adverse Events of Special Interest (AESI)

CRS
Cytokine release syndrome was not observed in extended follow-up of participants who had been analyzed previously, as this toxicity is typically seen in the first two weeks after CAR-T cell infusion.
All grade CRS occurred in 59% 3L+ FL subjects including Grade 3 CRS in 0.9%. CRS resolved in all subjects. No new subject developed late onset CRS.

Neurologic Toxicity (specific to the product class)
Out of 107 3L+ FL subjects treated with lisocel, all grade neurologic toxicity (NT) occurred in 15% (16/107) including grade 3 NT in 2%. All NT resolved with a median duration of 4.5 days (range: 1 to 17 days).

Prolonged Cytopenia
Prolonged cytopenia was defined at cytopenia which persisted beyond the Day 29 visit (+/- 2 day window as allowed by the study). Grade 3 or higher prolonged cytopenias persisted in 22% of FL patients, including thrombocytopenia in 14%, neutropenia in 16% and anemia in 34% of patients.

Serious Infections
Infections of any grade occurred in 22% of 3L+ FL patients treated with lisocel, with Grade 3 or higher occurring in 5.5% of patients.

Hypogammaglobulinemia
As of new data cutoff date, all grade hypogammaglobulinemia occurred in 6.5% (7/107) subjects.

MAS

One fatal case of MAS/HLH occurred in a 2L+ FL patient (reviewed during initial BLA review for FL). No new cases of MAS/HLH Occurred during extended follow up.

IRR
No new IRR; no new subjects were treated.

TLS
No new subjects were treated.

SPM
As of the March 31, 2025 data cutoff date, a total of 18 types of secondary malignancies reported in 23 subjects (Table 12

Table 12 Second Primary Malignancies, JCAR017-FOL-001 study

CANCER TYPE	N ROWS	% (N/107)
BASAL CELL CARCINOMA	3	3%
MELANOMA	2	2%
SQUAMOUS CELL CARCINOMA	2	2%
ACUTE MYELOID LEUKEMIA	1	1%
ACUTE MYELOID LEUKEMIA TRANSFORMATION	1	1%
BASAL CELL CANCER	1	1%
COLON ADENOCARCINOMA	1	1%
COLORECTAL CANCER	1	1%
HODGKIN LYMPHOMA	1	1%
MUCOEPIDERMOID CARCINOMA	1	1%
MYELODISPLASIA	1	1%
MYELODYSPLASTIC SYNDROME/MYELOPROLIFERATIVE NEOPLASM OVERLAP SYNDROMES (CONFIRMED)	1	1%
MYXOID SPINDLE CELL SARCOMA	1	1%
PROSTATE CANCER	1	1%
RECTAL CANCER	1	1%
SQUAMOUS CELL CARCINOMA (RIGHT SUPERIOR LATERAL NECK)	1	1%
SQUAMOUS CELL CARCINOMA IN SITU	1	1%
TREATMENT-RELATED ACUTE MYELOID LEUKEMIA	1	1%
SOURCE: FDA ANALYSIS ADSPM DATA, JCAR017-FOL001 STUDY		

For the new subjects who developed SPM during this extended follow up, tumor samples from 5 subjects (MDS [n = 2], mucoepidermoid carcinoma [n = 1], melanoma [n = 1], and SCC [n = 1]) were received for transgene testing, with 3 samples confirmed transgene negative by ISH (mucoepidermoid carcinoma, melanoma, and SCC). For the remaining 2 samples from 2 subjects, 1 sample was not evaluable for transgene by ISH due to no tumor cells being present in the tumor tissue (MDS, 4L+), and the other had insufficient sample quality (MDS, 3L).

Reviewer Team's comment: Patients with Follicular lymphoma have a risk of second primary malignancies that is higher than the cancer risk in the general population, with risks of SPM being reported between 9.3% and 26.1%.[1]

6.1.11.5 Clinical Test Results

Abnormal laboratory tests without clinical syndromes were rarely identified, and no specific trends were noted.

6.1.11.6 Dropouts and/or Discontinuations

As of the 31-Mar-2025 data cutoff, 106 (99.1%) subjects had completed the treatment period (Days 1 to 29) with 78 (72.9%) subjects that continued to and were ongoing in the Posttreatment Period (Day 30 to Month 60), 27 (25.2%) had discontinued with majority due to death (12 subjects, 11.2%), and 3 (2.8%) subjects transferred to the LTFU study, after completing primary follow-up. The cause of deaths for patients who discontinued is shown in **Error! Reference source not found.**

Table 13. Cause of death for subjects who discontinued due to death

SUBJID	SUBINFO1	COHORT	DCFURS	DTHDY	DTHCAUS
(b) (6)	80/M/BLK	4L+ FL	DEATH	1286	UNKNOWN
	76/F/WHT	4L+ FL	DEATH	114	SECONDARY MALIGNANCY (ACUTE MYELOID LEUKEMIA)
	57/F/NCU	4L+ FL	DEATH	474	ACUTE MYELOID LEUKEMIA
	53/F/NCU	4L+ FL	DEATH	171	HEART FAILURE
	68/M/WHT	4L+ FL	DEATH	1124	LYMPHOMA
	70/M/NCU	3L FL	DEATH	169	COVID-19
	53/M/WHT	3L FL	DEATH	971	SEPTIC SHOCK OF UNKNOWN ORIGIN

(b) (6)	49/M/WHT	3L FL	DEATH	12001	NEUTROPENIC SEPSIS SECONDARY TO CHEMOTHERAPY SECONDARY TO RETROPERITONEAL SARCOMA
	44/F/NCU	4L+ FL	DEATH	190	MOST LIKELY PML, THIS WAS PROGRESSIVE AND GRADE 4 ON 06APR2022
	64/M/WHT	4L+ FL	DEATH	180	NON-HODGKIN'S LYMPHOMA PROGRESSION
	55/M/WHT	4L+ FL	DEATH	1079	SEPTIC SHOCK IN PERSISTENCE OF MDS POST ALLOGRAFT
	70/M/WHT	3L FL	DEATH	551	COVID-19 PNEUMONIA
Source: FDA Analysis, ADSL data, JCAR017-FOL001 study					

6.1.12 Study Summary and Conclusions

Overall, during extended follow up, there were no new safety signals seen for 107 patients treated with lisocel in JCAR017-FOL001 study. New cases of secondary malignancies occurred, consisting of various solid and hematological malignancies (AML and MDS) generally known to occur in patients with relapsed refractory hematological malignancy with multiple prior lines of therapies including alkylating agents and radiotherapy. No new cases of T cell lymphoma occurred. Overall, the safety data is consistent with the data observed during initial BLA review for FL (with data cutoff date of January 27, 2023).

7. Integrated Overview of Efficacy

No additional studied beyond FOL-001 were reported for this supplement; and therefore, no integrated efficacy analysis was performed.

8. Integrated Overview of Safety

No additional studies beyond FOL-001 were reported for this supplement

8.1 Safety Assessment Methods

Not applicable

1 *Dinnessen. Blood Cancer Journal, 2021. 11(11): 179; Giri. Clinical Lymphoma Myeloma Leukemia, 2017.17(9): 569; Andrade-Campos. European Journal of Haematology, 2016. 97(6): 576*

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Not applicable

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Not applicable

8.2.3 Categorization of Adverse Events

Not applicable

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable.

8.4 Safety Results

8.4.1 Deaths

Not applicable

8.4.2 Nonfatal Serious Adverse Events

8.4.3 Study Dropouts/Discontinuations

Not applicable

8.4.4 Common Adverse Events

Not applicable

8.4.5 Clinical Test Results
Not applicable

8.4.6 Systemic Adverse Events

Not applicable

8.4.7 Local Reactogenicity

Not applicable

8.4.8 Adverse Events of Special Interest

See section 6

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

This was a late phase trial, with a single dose of lisocel administered. as such, there are no data on dose-dependency of adverse events.

8.5.2 Time Dependency for Adverse Events

The time course of adverse events in the entire population was like what is predictably seen with other CAR-T cell therapies, and did not differ in the 9 additional patients studied.

8.5.3 Product-Demographic Interactions

No appreciable differences were noted in different demographic groups

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

Liso-cel bears a boxed warning for T-cell lymphomas. Otherwise, the number of new primary malignancies was not unusual for the treated patient population.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.5.8 Immunogenicity (Safety)

Not reviewed

8.5.9 Person-to-Person Transmission, Shedding
Not applicable

8.6 Safety Conclusions

The safety of liso-cel on follow up was similar to what was observed in the initial application. The safety was broadly like that of other CAR-T cell products.

9. Additional Clinical Issues

9.1 Special Populations

No further analysis of special population was performed for this submission

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported.

9.1.2 Use During Lactation

No data were submitted on the use of Breyanzi during lactation.

9.1.3 Pediatric Use and PREA Considerations

Pediatric use was not addressed in this submission.

9.1.4 Immunocompromised Patients

The entire cohort of participants were immunocompromised by virtue of their lymphoid malignancy and the treatments for that disease. No specific further immunocompromised subgroup was analyzed.

9.1.5 Geriatric Use

Not separately analyzed

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

No additional clinical evaluation was performed.

10. CONCLUSIONS

The data submitted in this supplement continue to demonstrate favorable benefit risk of liso-cel for the indicated FL population. The extended follow up for all responders demonstrate durability of response, and in the context of high CRR and favorable safety profile denotes clinical benefit. The data from JCAR019-FOL-001 continue to demonstrate safety and substantial evidence of effectiveness and therefore supports conversion to a traditional approval of liso-cel for treatment of adults with relapsed refractory FL after at least 2 prior lines of systemic therapy.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Relapsed and Refractory Follicular Lymphoma (RR FL)

RR FL is a serious and life-threatening disease characterized by frequent relapse. With each relapse, the prognosis worsens with decreased response to current therapies. Median progression-free survival (PFS) decreases from 6.6 years in association with first line of therapy to 1.5 and 0.83 years with second- and third-line therapies, respectively (Link et. Al, Br J Haematol. 2019). Multiple lines of therapies can lead to cumulative toxicities and/or resistance to therapy, with possible transformation to high-grade or aggressive lymphomas leading to death.

Current treatment options include chemo-immunotherapy, high dose chemotherapy followed by autologous stem cell transplantation (SCT), EZH2 inhibitors, BTK inhibitor, bi-specific antibodies, CD19 CAR T cell therapy, or allogeneic SCT in selected cases. Although the ORR with currently approved drugs ranges from 34 to 91%, durability of response remains limited. Relapses following above therapies are challenging to treat, and therefore there is a need for new and effective therapies for patients with r/r FL.

Evidence and uncertainties

Study JCAR017-FOL-001 is a single-arm, multi-center international study which enrolled adult patients with r/r FL after ⩾ 1 line of systemic therapy. Subjects received a single infusion of lisocel following lymphodepletion. The primary endpoint was Overall Response rate (ORR) per Independent Review Committee. After an extended follow up with a data cutoff date March 31, 2025, the ORR was 91.1% (95% CI: 91.7, 99.4), CRR was 73.8% (05% CI: 64.2, 82.0). Median duration of response was NR (95% CI: 38.51, NR) after a median follow up of 35.38 months (95% CI: 35.06, 35.45). At the time of new data cutoff date, 63 subjects were in ongoing response.

During the extended follow up, there were no new safety signals observed; and the safety data is consistent with the safety data observed during initial BLA review for FL (with data cutoff date of January 27, 2023).

11.2 Risk-Benefit Summary and Assessment

The extended follow up of 3L+ FL subjects treated with lisocel in JCAR017-FOL001 study demonstrates durable ORR along with high CRR rate, and favorable benefit risk prolife in adult patients with r/r FL after at least two lines of systemic therapy is favorable. The efficacy and safety data denotes clinical benefit in 3L+ FL patients, and therefore support a traditional approval.

11.3 Discussion of Regulatory Options

1) Fulfillment of Accelerated Approval PMR:

The accelerated approval of liso-cel for follicular lymphoma (May 15, 2024) was based on results from Cohorts 1 and 2 of Study JCAR017-FOL-001 (TRANSCEND FL), entitled ‘A Phase 2, Open-label, Single arm, Multicohort, Multicenter Trial to Evaluate the Efficacy and Safety of JCAR017 in Adult Subjects with Relapsed or Refractory Indolent B-cell Non-Hodgkin Lymphoma (NHL)’ with the initial data cutoff date of January 27,

2023. The approval included a post marketing requirement (PMR) required according to the regulations for accelerated approval, 21CFR601.41 as below:

"*Collect and submit the final report, including datasets from the TRANSCEND FL clinical trial (NCT04245839) to verify and describe the clinical benefit of lisocabtagene maraleucel (BREYANZI) in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent). All partial and complete responders should have completed at least 24 months of follow up starting from the initial objective response*."

As agreed upon during the approval of lisocel for FL, the Applicant has completed the longer follow up for subjects in Cohorts 1 and 2 of JCAR017-FOL-001 study, i.e. at least 24 months for follow up for all responders since the onset of response. All responders (patients with best objective response of CR or PR), on continuing response, have completed at least 24 months of follow up for response since the time of onset of first response. The Applicant has submitted efficacy and safety data with extended follow up, and therefore has fulfilled AA PMR requirement.

2) Recommendation for conversion to traditional approval:
The clinical course of FL is characterized by repeated relapse and progressively shorted remissions with each successively lines of systemic therapy. There is no consensus on standard of care for 3L+ FL patients. With the exception of approved CD19 CAR T therapies, other treatments require prolonged duration of therapy, and the outcome and survival generally worsens with each line of therapies.

Cohort 1 and 2 of JCARFOL017-FOL-001 study enrolled relapsed refractory FL patients who have received two or more prior lines of systemic therapy: 49/114 43%) had received 3 prior lines (3L FL) and 65/114 (57%) had received 3 or more prior lines of systemic therapy (i.e. 4+L FL). Treatment with a single administration of lisocel resulted in durable ORR along with high CRR. The safety and efficacy data from JCAR019-FOL-001 with extended follow up continue to demonstrate favorable benefit risk of liso-cel for the indicated FL population. The extended follow up for all responders demonstrate durability of response, does not show new safety signal and in the context of high CRR, one-time treatment and favorable safety profile denotes clinical benefit in this advanced multiple relapsed or refractory FL population. The data from JCAR019-FOL-001 continue to demonstrate safety and substantial evidence of effectiveness and therefore supports conversion to a traditional approval of liso-cel for treatment of adults with relapsed refractory FL after at least 2 prior lines of systemic therapy.

11.4 Recommendations on Regulatory Actions

Based on the review of efficacy and safety data submitted with this BLA supplement, the review team recommends following

1. The Applicant has completed accelerated approval PMR study as agreed and noted in May 15, 2024 Approval letter of Breyanzi for Follicular lymphoma. Specifically, the Applicant has submitted final study report (CSR) including datasets from JCAR0147-FOL-001 including at least 24 months of follow up for response for all responders.

2. Data from JCAR017-FOL-001 continue to show positive benefit risk of lisocel in adult patients with relapsed refractory FL after 2 or more prior lines of systemic therapy. The ORRs are durable, and in the context of high CRR and manageable safety profile denote clinical benefit in the indicated population. These data supports conversion of an accelerated approval of lisocel to a traditional approval for treatment of adult patients with relapsed refractory follicular lymphoma after 2 or more prior lines of systemic therapy.

11.5 Labeling Review and Recommendations

Several revisions were made to the Applicant's proposed United States Prescribing Information. Please see Table 13 below for a summary of significant changes to the United States Prescribing Information.

Table 14 Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	Accelerated approval statement deleted	FDA agreed to removal of accelerated approval statement for Follicular lymphoma indication based on long-term follow-up data from Study 5 (Relapsed or Refractory FL Cohort).
Section 6 Adverse Reactions	-	Revised to update footnotes in adverse reaction Tables for concise presentation of data.
Section 12 Clinical Pharmacology	Updates to include Pharmacokinetics data from the long-term follow-up.	FDA agreed to include Pharmacokinetics data.
Section 14: Clinical Studies	Section 14.3 updated to add patient information and efficacy data from long-term follow-up.	FDA agreed to update patient information and data from long-term follow-up. However, the 18-month data was removed from efficacy Table 26. Multiple landmark timepoints for DOR estimate are not informative to the

		prescribers and are considered promotional. Therefore, landmark analyses were restricted to 2 timepoints, 12 months and 24 months.

Source: Created by FDA Clinical Review Team and Associate Director for Labeling