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BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Efficacy Supplement BLA
Application Number(s)	125714/225
Priority or Standard	Priority
Submit Date(s)	November 21, 2023
Received Date(s)	November 22, 2023
PDUFA Goal Date	May 23, 2024
Division/Office/Center	DCEH/OCE/CBER
Review Completion Date	May 8, 2023
Established Name	Lisocabtagene maraleucel
Trade Name	BREYANZI
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Applicant	Juno Therapeutics
Formulation(s)	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+ CAR T+ cells and CD8+ CAR T+ cells in separate syringes.
Dosing Regimen	90 to 110 × 10^6 CAR-positive viable T cells, administered by intravenous infusion, and preceded by conditioning chemotherapy
Applicant Proposed Indication(s)/Population(s)	adult patients with follicular lymphoma (FL) who have: (b) (4) • relapsed or refractory disease after 2 or more lines of systemic therapy
Recommendation on Regulatory Action	accelerated approval
Recommended Indication(s)/Population(s)	adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more lines of systemic therapy

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MORE = Medical Oncology Review
MHB = Malignant Hematology Branch
DCEH = Division of Clinical Evaluation Hematology

Glossary

Abbreviation	Definition
2L	Having received one line of prior therapy for the disease under study (second-line treatment)
2L+	Having received one or more line of therapy for the disease under study (second-line or later treatment)
3L	Having received two lines of prior therapy for the disease under study (third-line treatment)
3L+	Having received two or more lines of prior therapy for the disease under study (third-line or later treatment)
4L+	Having received three or more lines of prior therapy for the disease under study (fourth-line or later treatment)
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukemia
ATA	Anti therapeutic antibody
AUC	Area under the blood concentration-time curve
BLA	Biologics License Application
BMB	Bone marrow biopsy
BMS	Bristol-Myers Squibb Company
B-NHL	B-cell non-Hodgkin's lymphoma
BOR	Best overall response
BTKi	Bruton tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
cfDNA	Cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CHOP	Cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone
CI	Confidence interval
CLL	chronic lymphocytic leukemia
Cmax	Maximum observed blood concentration
CMR	Complete metabolic response
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRMTS	Center for Biologics Evaluation and Research (CBER) Regulatory Meetings Management Tracking System
CRO	Clinical research organization
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computerized tomography
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer - Quality of Life C30 questionnaire
EOS	End of study
EQ-5D-5L	European Quality of Life-5 Dimensions health state classifier to 5 levels
ESMO	European Society of Medical Oncology
FACT-LymS	Functionality Assessment of Cancer Therapy Lymphoma Subscale
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GBDS	Global Biometric and Data Sciences
GCP	Good clinical practice
GCSF	Granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GM-CSF	Granulocyte macrophage colony-stimulating factor
HGBCL	High grade B cell lymphoma
HLH	Hemophagocytic lymphohistiocytosis
HRQoL	Health-related quality of life

Abbreviation	Definition
HSCT	Hematopoietic stem cell transplantation
ICF	Informed consent form
ICH	International Council on Harmonisation
ICU	Intensive care unit
IgG	Immunoglobulin
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
IND	Investigational New Drug
iNHL	Indolent non-Hodgkin lymphoma
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISA	Insertion site analysis
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LDH	Lactate dehydrogenase
Liso-cel	Lisocabtagene maraleucel
LSLV	Last subject last visit
LTFU	Long term follow-up
MALT	Mucosa-associated lymphoid tissue
MAS	Macrophage activation syndrome
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
MZL	Marginal zone lymphoma
N.A.	Not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NOS	Not otherwise specified
NT	Neurotoxicity/neurologic toxicity
ODD	Orphan Drug Designation
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI3K	Phosphoinositide 3 kinase
PK	Pharmacokinetic(s)
PMBCL	Primary Mediastinal Large B Cell Lymphoma
PML	Progressive multifocal leukoencephalopathy
PMR	Partial metabolic response
PMR	Post-marketing requirement
POD24	Progression of disease within 24 months of initial diagnosis chemoimmunotherapy with anti CD20 and alkylating agent
POD24-Per protocol	As per protocol definition and case report form: progression of disease within 24 months of diagnosis after initiating treatment with an anti-CD20 and alkylating agent within the first 6 months of initial FL diagnosis
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PRR	Partial response rate
PT	Preferred term
PVS	Persistence vector sequence
Q1	First quartile
Q3	Third quartile
QoL	Quality of life
R2	Rituximab and lenalidomide
RCL	Replication-competent lentivirus
RCR	Replication-competent retrovirus
RCT	Randomized clinical trial
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisone
REMS	Risk evaluation and mitigation strategy
R/R	Relapsed or refractory
SAE	Serious adverse event
SAP	Statistical analysis plan
sBLA	Supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SD	Stable disease
SE	Standard error
SLL	small lymphocytic lymphoma
SLR	Systematic literature review
SOC	System organ class
SPD	Sum of perpendicular diameter
SPM	Second primary malignancy
TARC	Chemokine (C-C motif) ligand 17
T-cell	T-lymphocyte
TEAE	Treatment-emergent adverse event
THRBCL	T cell/histiocyte-rich large B-cell lymphoma

Abbreviation	Definition	Abbreviation	Definition
TLS	Tumor lysis syndrome	US	United States
Tmax	Time of maximum observed blood concentration	USPI	United States prescribing information
TNE	Transplant non-eligible	VAS	Visual analog scale(s)
ULN	Upper limit normal		

1 Executive Summary

1.1 Product Introduction

On November 21, 2023, Juno Therapeutics (the Applicant) submitted a supplemental Biologics License Application (sBLA), seeking a new indication for BREYANZI (lisocabtagene maraleucel, hereafter referred to as liso-cel) for the treatment of adult patients with follicular lymphoma (FL) who have:

(b) (4) or

- Relapsed or refractory disease after 2 or more lines of systemic therapy

The proposed dose of liso-cel is a single intravenous infusion of 90 to 110 × 10^6 chimeric antigen receptor (CAR)-positive viable T cells, preceded by fludarabine and cyclophosphamide for lymphodepletion.

FL is an indolent type of non-Hodgkin lymphoma (NHL) which accounts for 20% of all NHL in the United States. As a B-cell disorder, FL expresses the surface antigens cluster of differentiation (CD)19 and CD20, among others. The disease is further characterized by an overexpression of the apoptosis regulator B-cell lymphoma 2, driven by the t (14;18) translocation found in 85% of cases. The frontline treatment involves chemoimmunotherapy including a CD20 directed therapy. Although 40 to 80% of patients achieve a CR to frontline chemoimmunotherapy, relapse over time is nearly universal, and prognosis progressively worsens with each recurrence. Additionally, transformation to the aggressive disease, diffuse large B-cell lymphoma (DLBCL), is a well-described phenomenon which eventually leads to death.

Liso-cel is a CD19-directed genetically modified cellular immunotherapy consisting of autologous T cells that have been transduced with a lentiviral vector encoding a CAR consisting of anti-CD19 single-chain variable fragment (scFv), a CD28 effector domain, and a 4-1BB co-stimulatory domain. It is currently approved for treatment of adult patients with:

1) R/R large B-cell lymphoma (LBCL) after 2 or more lines of systemic therapy, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B (traditional approval on February 5, 2021).

2) LBCL, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B (traditional approval on June 24, 2022):
   a) Disease refractory to first-line chemoimmunotherapy or who relapse within 12 months of first line chemoimmunotherapy; or
   b) Disease 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, and

3) R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase inhibitor (BTKi) and a B-cell lymphoma 2 inhibitor (accelerated approval on March 14, 2024).

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant's request for approval is based on demonstration of substantial evidence of effectiveness in Study JCAR019-FOL-001 (TRANSCEND FL, hereafter referred to as Study FOL-001). Study FOL-001 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 NHL. 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). Among the 94 subjects included in the Food and Drug Administration (FDA)'s primary efficacy analysis, the median age was 63 years (range: 30 to 80), 63% were male, 55% were White, 3% were Black, and 9% were Asian, 89% had Stage III to IV disease, 29% had bulky disease, 30% had a prior autologous hematopoietic stem cell transplantation, and 50% had progression of disease within 24 months of initial diagnosis (POD24). The median number of prior therapies was 3 (range: 2 to 10). Between leukapheresis and administration of liso-cel, 37 patients (39%) received bridging chemotherapy. The subjects were treated with a single dose intravenous infusion of liso-cel with a target dose of 90 to 110 × 10^6 CAR-positive viable T cells. The median dose administered was 100.02 × 10^6 CAR-positive viable T-cells (range: 93.4 to 109.2 x 10^6 CAR-positive viable T cells).

Efficacy

Efficacy was established based on ORR per IRC based on Lugano 2014 criteria (Cheson et al. 2014). The ORR was 96% (95% CI: 90, 99) with a median time to response of 1.0 months (range 0.6 to 3.3). Median duration of response (DOR) was not reached (95% CI: 18.0, not evaluable [NE]) with a median duration of follow-up of 16.8 months (95% CI: 16.3, 17.0). The CR rate was 73% (95% CI: 63, 82) with a median time to first CR of 3 months (range: 0.6 to 18.0). In the 114 Leukapheresed patients, ORR was 92% (95% CI: 86, 96) with a CR rate of 68% (95% CI: 59, 77) and a partial response (PR) rate of 24% (95% CI: 16, 33).

The high ORR observed in FL patients treated with liso-cel in FOL-001 Study compares favorably to ORRs seen with available therapies with traditional approval, which ranges from 59% to 80% (see Section 2.2). Furthermore, the ORR also compares similarly with available therapies with accelerated approval, which range from 34% to 91%. The CR rate of liso-cel in this patient population also compares favorably with available

therapies.

Safety

The FOL-001 study was the primary source for safety data and included a total of 107 subjects with R/R FL who had received at least 2 prior systemic therapies and were treated with liso-cel. Grade 3 or higher adverse events (AEs) occurred in 83 (76%) subjects. Adverse events of special interest included: cytokine release syndrome (CRS) (59%) with Grade ≥3 CRS in 1.9% of patients; neurologic toxicities (15%) with Grade 3 in 2%; prolonged cytopenia (Grade ≥3 thrombocytopenia in 14% and Grade ≥3 neutropenia in 16%) and Grade ≥3 anemia 34%; infections in 22% with Grade ≥3 infections in 5.5% and hypogammaglobulinemia in 26%.

CRS and neurologic toxicities are acute and serious risks associated with liso-cel. The product has a boxed warning for these toxicities along with a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU). The other identified risks included in the Warning and Precautions section of the label are immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), serious infections, prolonged cytopenias, hypogammaglobulinemia, and secondary malignancies.

Secondary malignancy, particularly T-cell malignancy, is a risk following treatment with CD19 and B-cell maturation agent-directed immunotherapies, including liso-cel. The current liso-cel United States prescribing information (USPI) includes a boxed warning for T cell malignancies. There were no events of replication-competent retrovirus (RCR) infection or insertional mutagenesis reported in this sBLA. Long-term safety after treatment with liso-cel, particularly from the risk of insertional mutagenesis related to secondary malignancies, remains a concern. Therefore, a post-marketing requirement (PMR) for a long-term follow-up (LTFU) registry study up to 15 years is warranted.

Conclusion

Study FOL-001 represents an adequate and well-controlled trial. The magnitude of benefit based on high response rate and DOR in the proposed population forms the basis for substantial evidence of effectiveness in the context of an acceptable safety profile. Given the disease setting of R/R FL, which may afford the potential for prolonged survival and multiple therapeutic interventions, concerns remain with the limited follow-up for DOR and ultimate clinical benefit. Therefore, the review team recommends an accelerated approval of liso-cel for the treatment of adults with R/R FL after 2 or more prior lines of systemic therapy, with a requirement for a confirmatory study to verify the clinical benefit.

For verification of clinical benefit, two potential options were considered: 1) a randomized trial with a time-to-event endpoint such as PFS or overall survival (OS) or 2) additional follow-up of the current patients in Study FOL-001. The additional follow-up of

at least 24 months for DOR in Study FOL-001 was selected to verify the clinical benefit of liso-cel in the indicated population based on the following rationale:

- 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 NHL, including data from a randomized controlled trial.
- There is no established standard of care for patients with R/R FL receiving third line treatment and beyond, however there are multiple therapeutic interventions that may be considered.
- In patients with R/R FL, outcome with each successive line of therapy is worse, leading to higher mortality after each treatment (see Section 2.1).
- The availability of liso-cel and two other CAR T products under accelerated approval for third line treatment of R/R FL may impact the feasibility of accruing and completing a randomized trial.

Of note, the Applicant provided safety and efficacy data for (b) (4) (b) (4) to support a proposed indication. (b) (4) (b) (4) he data were determined to be insufficient to support an approval for this indication.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment for lisocabtagene maraleucel (liso-cel) for the indicated population is based on the results of JCAR017-FOL-001, 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 NHL. A total of 94 patients with R/R FL after two of more prior lines of systemic therapies constituted the efficacy analysis population. The primary efficacy endpoint is ORR determined by IRC as per 2014 Lugano Criteria (Cheson et al. 2014). Key secondary efficacy outcome measures included DOR and CR rate.

JCAR017-FOL-001 study demonstrated high ORR of 96% (95% CI: 90, 99) with durability of response in adult patients with R/R FL after 2 or more prior lines of systemic therapies.

The safety profile of liso-cel in the treatment of adults with R/R FL is consistent with the safety profile in the other approved indications. CRS or neurologic toxicity (NT) can be life-threatening or fatal and requires institution of a REMS. Some patients may develop IEC-HS, which could result in a fatal outcome. Hypogammaglobulinemia may predispose patients to serious infection and require monitoring and intervention. Prolonged cytopenias may increase the risk of serious infections and require transfusion or growth factor support. These risks can be managed with appropriate monitoring and mitigation strategies in place. Therefore, these AEs represent toxicities that are acceptable from a benefit-risk perspective in the intended population. Thus, the overall benefit-risk prolife of liso-cel in adult patients with R/R FL after at least 2 lines of systemic therapy is favorable and supports accelerated approval. The clinical benefit should be confirmed by additional follow-up of responders in JCAR017-FOL-001 Study for at least 24 months from the time of first response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• FL is an indolent form of NHL, characterized by frequent relapse. With each relapse, the prognosis worsens with decreased response to current therapies.	• R/R FL is a serious and life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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. 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	• Current treatment options include chemo-immunotherapy, high dose chemotherapy followed by autologous stem cell transplantation (SCT), EZH2 inhibitors, BTKi, 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.	• The available treatment options for patients with R/R FL remain limited. • Many patients relapse after these therapies which results in decreased response to subsequent therapies. • There is a need for new and effective therapies for patients with R/R FL.
Benefit	• 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 liso-cel following lymphodepletion. • The primary endpoint was Overall Response rate (ORR) per Independent Review Committee. • In the efficacy analysis set (N=94), the ORR rate was 96% [95% CI: 90, 99] • Complete response rate (CRR) was 73% (95% CI: 63, 82). • With a median follow-up of 16.8 months, the median DOR was not reached [95% CI: 18.04, NE] • The median time to first response was 1.0 month (range: 0.6 to 3.3 months)	• The high ORR, supported by CRR, with durability of response, provides robust evidence of clinically meaningful activity in patients with R/R FL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The serious adverse events were CRS, NT, IEC-HS, prolonged cytopenia, hypogammaglobulinemia, serious infections, and secondary malignancies. • CRS and NT can be mitigated by requirement of REMS, careful site selection and training of investigators. • There is a theoretical risk of secondary malignancy due to RCR or insertional mutagenesis. There were no such cases during this study as of the data cutoff date.	• The evidence suggests that the clinical benefit outweighs the risk of liso-cel in adult patients with R/R FL. • The risks associated with liso-cel warrant a boxed warning for CRS and NT, a REMS with ETASU, and a long-term follow-up study.

1.4 Patient Experience Data

The Applicant submitted patient reported outcomes (PROs) collected using three different instruments (FACT-LymeS questionnaire, EORTC QLQ-C30 questionnaire and EQ-5D Utility Index). However, because the study is a single arm study with no comparator, the PRO data is descriptive and is not considered for regulatory decision making.

Patient Experience Data Relevant to this Application (check all that apply)

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Section 8.1.2
☐	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	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
FL is the most common subtype of iNHL in the US, accounting for approximately 70% of the iNHL, and the second most common type of NHL, accounting for about 20% of all NHL cases.[1] 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.[2]

FL is a heterogeneous pathological entity that includes tumors derived from germinal center B-cells, both centrocytes and centroblasts. The t(14;18) translocation has been recognized as a genetic hallmark of FL and results in constitutive overexpression of the BCL-2 protein. The disease is characterized by diffuse lymphadenopathy, bone marrow involvement, splenomegaly, and other less common sites of extranodal involvement. Histologically, FL is classified as grade 1, grade 2, and grade 3 (3A and 3B) depending on the percentage of the large lymphocytes present.[3] 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.[4] 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, lactate dehydrogenase, and β2 microglobulin. These prognostic factors are included in the commonly used FLIPI and FLIPI-2 prognostic indices.[5,6] FLIPI was highly predictive of treatment outcomes and separated patients into 3 distinct risk groups with 10-year OS rates of 70.7% (low risk; 0-1 risk factor), 50.9% (intermediate risk; 2 risk factors), and 35.5% (high risk; ≥ 3 risk factors), respectively.[5] In patients with relapsed disease, the types of prior treatments and duration of response to prior treatments may be more important in predicting the outcomes of subsequent treatments.[7]

Despite the introduction of novel agents, including immunotherapies, FL remains an incurable malignant disease. Although initially an indolent disease sensitive to a variety of chemotherapeutic agents, FL exhibits a continuous pattern of relapses with decreasing sensitivity to chemoimmunotherapy leading to a poor outcome. A particularly poor prognostic group are patients that progress within 24 months of initiation of front-line chemoimmunotherapy, consisting of a combination of an alkylating agent and an anti-CD20 monoclonal antibody, referred to in this document as POD24 to distinguish it from an alternative POD24 definition published by Casulo et al, in 2015 and used in the FOL-001 protocol (POD24-Per protocol) which refers to progression relative to diagnosis. That study reported a 5-year OS of 50% in patients with FL meeting this POD24 definition per Casulo, as compared to 90% in patients with FL that did not.[8] Similarly, patients meeting the POD24 definition have a poor prognosis compared to patients without POD24 after standard chemoimmunotherapy regimens.[1] Tumor burden defined by GELF is widely used to define patients in whom immediate therapy is

necessary. A small Japanese study has reported lower PFS in patients that meet different variations of the GELF criteria.[9] The development of more efficacious therapies for patients with R/R FL especially for patients with high-risk disease is therefore an imperative.

The FDA's Assessment:

FDA agrees with Applicant's position.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Table 1: Applicant - Drugs Approved by the FDA for the Treatment of Patients With R/R FL

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint (s)[a]	Trial Design (Study)/ Results
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)[b]	Treatment of adult patients with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy	ORR	Single-arm study (ZUMA-5) ORR: 91.4%; CRR: 60.5% Median DOR: not estimable Median of 3 prior lines of therapy
Ukoniq™ (umbralisib)[g] Kinase inhibitor **Withdrawn from market on 31-May-2022 due to safety concerns**	Accelerated (05-Feb-2021)[b]	Treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least 3 prior lines of systemic therapy	ORR	Single-arm cohort (UTX-TGR-205) ORR: 42.7%; CRR: 3.4% Median DOR: 11.1 mo Median of 3 prior lines of therapy
Tazverik® (tazemetostat) Methyltransferase inhibitor	Accelerated (18-Jun-2020)[b]	• Treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-	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

Table 1: Applicant - Drugs Approved by the FDA for the Treatment of Patients With R/R FL

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint (s)[a]	Trial Design (Study)/ Results
		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		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[e]
Copiktra® (duvelisib) Kinase inhibitor **FL indication withdrawn on 13-Apr-2022**	Accelerated 24-Sep-2018[b]	Treatment of adult patients with relapsed or refractory FL after at least 2 prior systemic therapies	ORR	Single-arm study (NCT02204982) ORR: 42.2%; CRR: 1.2% Median DOR: not reached Median of 3 prior lines of therapy
Aliqopa® (copanlisib) Kinase inhibitor	Accelerated (14-Sep-2017)[b]	Treatment of adult patients with relapsed follicular lymphoma who have received at least 2 prior systemic therapies	ORR	Single-arm study (CHRONOS-1) ORR: 58.7%; CRR: 14.4% Median DOR: 12.2 mo Median of 3 prior lines of therapy
Rituxan Hycela® (rituximab and hyaluronidase human) Combination of a CD20-directed cytolytic antibody and an endoglycosidase	Traditional 22-Jun-2017	Relapsed or refractory, follicular lymphoma as a single agent	Not reported	Not provided in label[f]
Gazyva® (obinutuzumab) CD20-directed cytolytic antibody	Traditional 26-Feb-2016	In combination with bendamustine (Ben) followed by obinutuzumab (Obin) monotherapy for	PFS	RCT: Obin + Ben followed by Obin vs Ben (GADOLIN) Median PFS: not reached vs 13.8 mo (HR = 0.48)

Table 1: Applicant - Drugs Approved by the FDA for the Treatment of Patients With R/R FL

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint (s)[a]	Trial Design (Study)/ Results
		the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen		ORR: 78.7% vs 74.7% CRR: 15.5% vs 18.7% Median DOR: not reached vs 11.6 mo Median of 2 prior lines of therapy
Zydelig® (idelasib) Kinase inhibitor **FL indication withdrawn on 26-May-2022**	Accelerated 23-Jul-2014[b]	Treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma who have received at least 2 prior systemic therapies	ORR	Single-arm study (NCT01282424) ORR: 54.2%; CRR: 8.3% Median DOR: not evaluable Median of 4 prior lines of therapy
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
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
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	3 single-arm studies (median number of prior lines of therapy not reported) 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

[a] Endpoint(s) on which the approval was based.
[b] Approved under 21 CFR 314 Subpart H or 21 CFR 601 Subpart E.
[c] Nine subjects with grade 3B or transformed FL were enrolled in this study: 3/45 (7%) patients in Cohort 4 and 6/54 (11%) patients in Cohort 5.[10] Of the 3 patients with grade 3B or transformed FL in the EZH2 mutated cohort, all had a response (all partial responses). Two (33%) of the 6 patients with grade 3B or transformed FL in the EZH2 wild-type cohort had a response (both partial responses).
[d] Not reported in prescribing information; from primary publication.[11]
[e] Not reported in prescribing information; from primary publication.[12]
[f] Approval was based on multiple randomized controlled trials demonstrating the following: (a) noninferior rituximab trough concentrations levels for Rituxan Hycela 1400 mg/23,400 Units compared to an

intravenous rituximab 375 mg/m^2 (b) noninferior rituximab Ctrough levels for Rituxan Hycela 1600 mg/26,800 Units compared to intravenous rituximab 500 mg/m^2 and (c) comparable efficacy and safety results of the 2 products.

Note: Table includes drugs approved since 1997 and does not include drugs approved to treat patients with grade 3B FL.

SLR Results

An SLR was performed to identify the current evidence on the clinical efficacy and safety for approved as well as investigational therapies for the treatment of adult patients with R/R FL (grade 1-3a) in the 2L+ POD24, 3L+, and 4L+ populations.[13] The SLR searched studies published between 01-Jan-1998 and 17-Sep-2022 and identified 112 publications representing 60 unique studies. Among the treatments analyzed in these 60 studies were CAR T cell therapies (axicabtagene ciloleucel and tisagenlecleucel), T-cell engagers (mosunetuzumab, glofitamab, epcoritamab, odronextamab), HSCT (autologous and allogenic), PI3K inhibitors (copanlisib, duvelisib, idelalisib), lenalidomide, rituximab, obinutuzumab, and tazemetostat. Of the 60 studies, 33 (55%) were retrospective or prospective cohort observational studies, while 27 (45%) were clinical trials (randomized, non-randomized, and single arm). The majority of the studies (N = 48; 80%) reported findings for 3L+ FL patients, with limited data for 4L+ and 2L+ POD24 patients.

R/R FL patients who had received at least two prior lines of therapies (3L+) demonstrated highly variable ORR and CRR depending on the type of treatment used. The use of anti-CD20 antibody treatments such as rituximab resulted in ORR and CRR that ranged from 37%[14] to 76%[15] and 11%[16] to 47%[15], respectively, over a median follow-up period of 18 to 29 months. PI3K inhibitors, which have been voluntarily withdrawn in the US, yielded ORR and CRR ranging from 40%[17] to 83%[18] and 0%[19] to 26%[18], respectively, with a median follow-up of 20 to 40 months. HSCT showed ORR and CRR ranging from 59%[20] to 100%[21] and 40%[20] to 100%[22], respectively with a median follow-up period of 20 to 61 months. Recently, two CD19 CAR T-cell therapies (axicabtagene ciloleucel and tisagenlecleucel) and a bispecific CD20-directed CD3 T-cell engager (mosunetuzumab) have been granted accelerated approval in the US based on pivotal single-arm studies, showing higher ORR and CRR rates compared to conventional therapies. In the ZUMA-5 trial, axicabtagene ciloleucel achieved an ORR and CRR of 94% and 79%, respectively, at a median follow-up of 30.9 months (ORR and CRR of 91% and 60%, respectively, when documentation of a negative BMB after treatment was required).[23,24] Tisagenlecleucel, evaluated in the ELARA trial at a median follow-up of 28.6 months, demonstrated an ORR and CRR of 86% and 68%, respectively.[25,26] Mosunetuzumab, assessed in the GO29781 trial with a median follow-up of 27 months, showed an ORR and CRR of 78% and 60%, respectively.[27,28]

The median OS or median PFS was not reported or not reached in most studies. However, one observational study reported that the median OS for chemoimmunotherapies and anti-CD20 antibody ranged from 25 to 40 months.[29] The median follow-up period was not reported in this study. Two studies on PI3K inhibitors reported a median OS of 48[30] and 61[31] months and a median PFS of 8[30] and 11[31] months over a follow-up period of 20 and 40 months, respectively. For HSCT,

observational studies reported a median OS ranging from 10[21] to 85[32] months and a median PFS ranging from 12[22] to 58[33] months, with a median follow-up of up to 140 months. In the ZUMA-5 trial, median OS was not reached, and median PFS was 40 months after a median study follow-up of 42 months.[34] In the ELARA trial, median OS and median PFS were not estimable after a median study follow-up of 29 months.[25] In the GO29781 trial, median OS and median PFS were not reached after a median study follow-up of 27 months.[27]

Data were sparsely available for 2L+ POD24 population, with only 12 (20%) studies reporting on POD24 across various lines of therapy. Of these, five studies reported explicitly on a 2L POD24 population, five studies reported on 2L+ POD24 (with an unclear line of therapy) and two studies reported on the 3L+ POD24 population.

Among the five studies reporting results in a 2L POD24 population, only one observational study reported response rates for patients who received different treatments, including chemoimmunotherapies, anti-CD20 monotherapy, and HSCT. In this study, the ORR for patients treated with chemoimmunotherapies ranged from 58% to 85%, while the CRR ranged from 29% to 55%.[35] Patients treated with anti-CD20 monotherapy had an ORR of 59% and a CRR of 35%. Additionally, HSCT yielded an ORR of 59% and a CRR of 40%. These results were observed after a median follow-up duration of 74.4 months. All five studies reported various survival outcomes (median OS/PFS, OS/PFS rates). In one observational study, the median OS for patients treated with chemoimmunotherapies ranged from 27.4 months to 34.1 months.[35] Patients receiving anti-CD20 monotherapy had a median OS of 29.6 months. The median follow-up was not provided for this study. In another observational study, the median OS was not reached for patients who underwent HSCT at a median follow-up of 140.4 months.[32] The 5-year OS ranged from 47%[29] to 83%[35] for chemoimmunotherapies, from 50%[29] to 73%[35] for anti-CD20 monotherapy, and from 67%[35] to 77%[36] for HSCT. Additionally, the 2-year PFS rate ranged from 20%[35] to 27% for patients treated with chemoimmunotherapies. For those who received anti-CD20 monotherapy, the 2-year PFS rate was 38%[35], while for HSCT, the PFS rates were 23%[35] at 2 years and 43%[37] at 5 years.

In the 2L+ POD24 population, two clinical trials investigated the combination of lenalidomide with an anti-CD20 antibody (either rituximab or obinutuzumab), resulting in an ORR ranging from 65%[38] to 75%.[39] In the NCT04246086 trial, which involved mosunetuzumab combined with lenalidomide, three 2L+ POD24 patients achieved an ORR of 100% and a CRR of 66.7%.[40] In the NCT03075696 dose-escalation study, involving glofitamab either as monotherapy or in combination with obinutuzumab, 19 POD24 patients in the glofitamab arm had an ORR of 68% and a CRR of 58%, while 10 patients in the glofitamab plus obinutuzumab arm had an ORR of 100% and a CRR of 70%.[41] Regarding survival outcomes in the 2L+ population, lenalidomide plus rituximab had a reported median PFS of 27.4 months after a median follow-up of 40.6 months,[38] while for lenalidomide plus obinutuzumab, both the median PFS and OS were not reached after a median follow-up of 31.2 months.[39] Furthermore, an observational study

on auto-HSCT showed a 5-year OS rate of 85.4% with a median follow-up of 105.8 months.[42]

Two trials investigated response and survival outcomes for CAR T-cell therapy in 3L+ POD24 patients. In the ZUMA-5 trial, axicabtagene ciloleucel treatment resulted in a 92% ORR and a 75% CRR in 3L+ POD24 patients, with 24-month OS and PFS rates of 77.6% and 57.3%, respectively, at a median follow-up of 30.9 months.[43] In the ELARA trial, tisagenlecleucel treatment led to a CRR of 59.0% in 3L+ POD24 patients at a median follow-up of 17 months, and a 12-month PFS rate of 60.8% was observed at the same median follow-up.[44]

Acknowledging potential heterogeneity across studies and treatments, a meta-analysis was conducted on all identified studies in the SLR[13] on treatments recommended in NCCN or ESMO guidelines. Studies that involved unapproved therapies such as odronextamab, duvelisib, epcoritamab, copanlisib, and idelalisib were not included. For a meta-analysis to be considered possible, at least four studies that were similar enough were required. In the 3L+ setting, the meta-analysis, which employed a random effects model, yielded pooled estimates for the ORR of 70% (95% CI: 60, 81) and the CRR of 54% (95% CI: 38, 70). In the 2L+ POD24 setting, the meta-analysis based on a random effects model yielded pooled estimates for the ORR of 74% (95% CI: 58, 90) and the CRR of 51% (95% CI: 32, 70).

Performing a meta-analysis on the median OS and median PFS in 3L+ and POD24 settings was deemed unfeasible as there were fewer than four sufficiently similar studies reporting on these endpoints. However, in the 3L+ setting, it was possible to conduct meta-analyses for the 2-year and 3-year OS and PFS rates. Nevertheless, caution should be exercised when interpreting the results due to the limited number of studies available and the heterogeneity of treatments contributing to the 2-year and 3-year rates. The estimated 2-year OS rate was 74% (95% CI: 63, 86), and the estimated 3-year OS rate was 78% (95% CI: 75, 82). Additionally, the estimated 2-year PFS rate was 53% (95% CI: 47, 59), and the estimated 3-year PFS rate was 66% (95% CI: 56, 76).

A sensitivity analysis was conducted to investigate the influence of treatment types, excluding studies that focused on CAR T-cell therapies, T-cell engagers, and HSCT.[13] The analysis encompassed studies that examined various treatments such as rituximab, tazemetostat, obinutuzumab plus lenalidomide, and 90Y ibritumomab tiuxetan. In the 3L+ setting, sensitivity analyses resulted in ORR and CRR of 62% (95% CI: 48, 77) and 27% (95% CI: 13, 42), respectively. Conducting sensitivity analyses for response outcomes in 2L+ POD24 and survival outcomes in both populations was deemed unfeasible.

The results of this SLR revealed an evolving treatment landscape for FL. Emerging therapies, such as CAR T-cell therapies and T-cell engagers, exhibit potential in improving the effectiveness of treatment for patients in the 2L+ POD24 and 3L+ populations (see Table 1 for drugs approved by the FDA for patients with R/R FL).

Unmet Medical Need for Patients with R/R FL

R/R FL after rituximab-based chemoimmunotherapy is a serious, life-threatening disease that is largely incurable despite advances in treatment and represents a major therapeutic challenge. In the majority of patients, FL relapses multiple times with a pattern of decreased durability of remission with each subsequent line of therapy.[45]

3L+ Population

Patients who have already received at least 2 prior lines of systemic therapy, including one prior line of chemoimmunotherapy, comprise a population of unmet need, given that PFS and OS are shorter with subsequent progressions.[46,47] In a meta-analysis including 12 studies published from 2014 to 2020, the median PFS and OS were 10.3 and 54.4 months, respectively in subjects who received at least 2 prior lines of therapy and 8.4 and 40.6 months, respectively in subjects who received at least 3 prior lines of therapy. Few patients achieved CR (12.2%) in the ≥ 2 prior lines of therapies group of patients.[46]

2L High Risk Population

Because outcomes are poorer with each subsequent line of therapy in FL, one of the challenges is identifying as early as possible the patients with R/R FL that are less likely to achieve favorable outcomes with conventional therapies. These patients have high risk disease and are in need of alternate early line treatment options. Progression of disease within 24 months of diagnosis or 24 months after initiation of chemoimmunotherapy and failure to achieve event-free survival at 12 months after initial treatment with chemoimmunotherapy have been identified as prognostic indicators of poor survival.[1] There are no standard approaches for treating this group of patients with high risk R/R FL. In the recent observational cohort study from the Lymphoma Epidemiology of Outcomes Consortium, 196 grade 1 to 3A FL patients with POD24 (after first line chemoimmunotherapy) were treated with heterogenous treatments, including chemoimmunotherapy (CHOP and bendamustine-based), salvage HSCT, novel therapies including PI3K inhibitors, anti-CD20 monotherapies, lenalidomide-based immunotherapies, or radioimmunotherapy. Across all treatments, the ORR was 63% and CR rate was 37%. At a median follow-up of 6.2 years, 2-year PFS was 22% and 5-year OS was 71%.[48]

The GELF criteria are also clinically useful to guide decision for treatment in earlier lines of therapy (ie, frontline and 2L). These patients are identified as per NCCN criteria[1] to have higher tumor burden disease, in need of immediate therapy and have been suggested to have a lower PFS compared to the general FL patient population. Patients with FL who received chemoimmunotherapy in frontline and meet the GELF criteria when evaluated for 2L treatment thus also represent another high-risk group. A small Japanese study has reported lower PFS in patients that meet different variations of the GELF criteria and received R-CHOP as frontline treatment.[9] The AUGMENT study evaluating the efficacy of R2 (rituximab plus lenalidomide) versus rituximab monotherapy in 2L+ FL showed a lower median PFS of 28 months in subjects that met the GELF criteria (N = 77) compared to a median PFS not reached in subjects that did not meet the GELF criteria (N = 70) in the R2 arm. Similar results were also shown for the rituximab plus placebo arm with median PFS of 9.6 months in subjects that met the GELF criteria (N = 68) compared to median PFS of 16.6 months in subjects that did not

meet the GELF criteria (N = 80).[49]

FDA Approved Treatments

Recently, FDA has granted accelerated approvals for the treatment of adult patients with R/R FL after 2 or more lines of systemic therapy including bispecific CD20-directed CD3 T-cell engager (mosunetuzumab), CD19-directed CAR T-cells (tisagenlecleucel and axicabtagene ciloleucel), and EZH2 inhibitor (tazemetostat). CAR T-cell therapies targeting CD19 demonstrated high and durable responses in the treatment of various B cell lymphomas. The 2 CD19-directed CAR T-cell therapies, ie, tisagenlecleucel based on ELARA Phase 2 study[50] and axicabtagene ciloleucel based on ZUMA-5 Phase 2 study[23] demonstrated high ORR and CR rates. Although the results are promising, these therapies have only been granted accelerated approval by the FDA. Despite these treatment options for R/R FL, there is no standard of care for FL patients after at least 2 lines of therapy, and treatment options for patients with high-risk FL who relapse after rituximab-containing frontline regimens remain limited.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of available therapies for R/R FL as listed in Table 1 with following additions:

1) Zanubrutinib was granted an accelerated approval on March 7, 2024, in combination with obinutuzumab for treatment of R/R FL after 2 or more prior lines of therapies. The approval was based on data from a randomized controlled trial (N=217 randomized 2:1 to receive either zanubrutinib plus obinutuzumab or obinutuzumab alone). The efficacy was based on an ORR of 69% (95% CI: 61, 76) in obinutuzumab arm versus 46% (95% CI: 34, 58) in obinutuzumab arm.
2) On March 18, 2024, the FL indication (under accelerated approval) for copanlisib was voluntarily withdrawn since the required postmarketing trial did not verify the clinical benefit.

The clinical review team acknowledges the Applicant's summary of the metanalysis performed to inform the current evidence on the clinical efficacy and safety for approved as well as investigational therapies for the treatment of adult patients with R/R FL. Given the limitations of such analyses, including but not limited to the heterogeneity of trials with regard to their design, population, conduct and treatments, caution should be exercised in interpretation of these results. Therefore, these results were not reviewed for the purpose of regulatory decision making. However, the clinical review team agrees that new and effective therapies are needed for treatment of R/R FL.

As described by the Applicant, the treatment of R/R FL varies depending on prior therapies, length of remission, patient age, fitness and comorbidities, and physician/patient preferences. In general, National Comprehensive Cancer Network 2023 guidelines (NCCN 2023) recommend the following approach:

Table 2. FDA Reviewer – Current Treatment Approach for R/R Follicular Lymphoma (2023 NCCN Guidelines)

Second-Line Therapy (Preferred regimens)	Third-Line And Subsequent Therapy
Preferred regimens (in alphabetical order) Bendamustine+ obinutuzumab or rituximab CHOP + obinutuzumab or rituximab CVP + obinutuzumab or rituximab Lenalidomide + rituximab Other recommended regimens Lenalidomide (if not a candidate for anti-CD20 mAb therapy) Lenalidomide + obinutuzumab Obinutuzumab Rituximab	Small molecule inhibitors PI3K inhibitor Copanlisib *EZH2* inhibitor Tazemetostat (irrespective of *EZH2* mutation status) T cell mediated therapy Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy Axicabtagene ciloleucel Tisagenlecleucel Bispecific T-cell engager therapy Mosunetuzumab-axgb

Source: FDA reviewer's analysis based on 2023 NCCN Guidelines (NCCN 2023): B-cell lymphomas

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

On 05-Feb-2021, BREYANZI was approved by the FDA for the treatment of adult patients with R/R LBCL after two or more lines of systemic therapy, including DLBCL NOS (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL grade 3B (BLA 125714/0; submitted on 18-Dec-2019). On 24-Jun-2022, BREYANZI was approved for the treatment of adult patients with LBCL, including DLBCL NOS (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL grade 3B, who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first line chemoimmunotherapy (sBLA 12571/90; submitted on 23-Dec-2021).

Liso-cel is exempt from pediatric study requirements for the indications for which it was granted ODD, including FL, per PREA and 21 CFR 314.55 (d).

The FDA's Assessment:

The review team agrees with Applicant's summary of regulatory history. Additionally, on March 14, 2024, the FDA granted accelerated approval to liso-cel for the treatment of adult patients with relapsed or refractory CLL or SLL who have received at least 2 prior lines of therapy including a BTKi and a BCL(b) (4)inhibitor.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Key FDA interactions under BB-IND 016506 related to the development of liso-cel in FL are summarized in Table 3.

Table 3: Applicant - 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 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)	• 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. • 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	• 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

Table 3: Applicant - Summary of Major IND Regulatory Activities Relating to FL Development

Date	Activity and Purpose	FDA Feedback
	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	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 (ie, nodal, extranodal, and splenic) in the study population. • 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.

Table 3: Applicant - Summary of Major IND Regulatory Activities Relating to FL Development

Date	Activity and Purpose	FDA Feedback
07-Aug-2023	Type B pre-sBLA Meeting: Request for pre-sBLA meeting submitted 05-Jun-2023 CRMTS#15052	• FDA confirmed that the Sponsor's proposals for narratives, table of contents, and clinical pharmacology data appear to be acceptable. • FDA strongly recommended a minimum of 12 months follow-up for DOR in all responders to inform the durability of the treatment effect and the benefit/risk determination. • FDA disagreed with the proposed criteria for the efficacy primary analysis and the terminology proposed for the criteria. Primary analysis should follow Lugano criteria including evaluation of the bone marrow with BMB results, and analyses without these results should be called sensitivity analyses. Based on the FDA feedback, the Sponsor will clearly label criteria and analyses in the sBLA submission. • Efficacy Analysis: FDA generally agreed with the structure and content of the datasets for Study FOL-001, and reiterated their request from the 2022 Type C meeting for an integrated efficacy analysis dataset, detailed reasons for censoring of DOR in the efficacy datasets, and detailed reasons for any unevaluable patients in an efficacy determination. • Post-market Registry Study: FDA agreed with the proposal for the study. Sample size should be based on the number of patients likely to be treated in a 5-year period. The protocol should be submitted with the sBLA, and include proposed enrollment criteria, enrollment size rationale, and milestone dates in the concept protocol. FDA agreed with the pharmacovigilance plan. FDA agreed that a major REMS modification is required for that in the current BLA, and agreed with the proposal to submit changes with the sBLA. • Confirmatory study: FDA stated that not having a confirmatory trial underway at the time of sBLA submission would not result in a Refuse to File. "Underway" may be defined as protocol submission to the IND and IRB approval. However, there would be significant approvability risk (Complete Response) if the trial was not well underway at the time of regulatory action. FDA clarified that the advice on timing of confirmatory study is consistent to all sponsors. FDA suggested that the confirmatory trial be started according to its 2021 advice prior to sBLA submission, and the protocol could be amended later to include a new population. BMS reiterated its commitment to executing a confirmatory Phase 3 trial, taking into account advice received from FDA in 2021. • FDA acknowledged that the liso-cel has been granted an orphan drug designation for treatment of FL, and therefore is not subject to PREA for this indication, and submission of a pediatric assessment is not required.

The FDA's Assessment:

FDA does not agree with the Applicant's statement "Underway may be defined as protocol submission to the IND and IRB approval". During Type B meeting (CRMTS # 15052), FDA stated that "For an application being considered for accelerated approval, the determination of whether a confirmatory trial is well under way will occur at the time of regulatory action."

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Compliance and Biologics Quality (OCBQ)

Not applicable

4.2 Product Quality

There are no outstanding issues with product quality.

4.3 Devices and Companion Diagnostic Issues

Not applicable

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

No new nonclinical pharmacology/toxicology data were provided in this submission.

6 Clinical Pharmacology

The Applicant's Position:

Pharmacokinetics, pharmacodynamics, and immunogenicity from R/R FL Cohorts 1 (4L+), 2 (3L), and 3 (2L) were evaluated in Study JCAR017-FOL-001 (hereafter referred to as Study FOL-001).

Results in the 2L+ group (Cohorts 1, 2, 3) are highlighted in this section.

Clinical Pharmacokinetics

Overall, liso-cel concentration in peripheral blood over time showed a similar pattern in the 4L+, 3L, and 2L groups. In all 3 groups, the liso-cel concentration in the peripheral blood detected by PCR exhibited a rapid expansion followed by a monophasic decline up to 28 days after infusion.

In the 2L+ group, median Cmax, AUC(0-28) and Tmax were 42026 copies/µg, 260274 day*copies/µg, and 10.0 days, respectively. Persistence of the liso-cel transgene was observed up to Day 730.

In the 2L+ group, no relevant differences in transgene PK parameters (Cmax, Tmax, AUC[0-28]) by subgroups (eg, age, sex, region, bulky disease [defined as any tumor nodal mass > 7 cm, or 3 or more nodal sites [each > 3 cm] at screening based on investigator assessment], pre-LDC SPD status per IRC, FLIPI risk category and modified GELF criteria) were observed, except for Tmax with either bulky disease or FLIPI risk category. A potential association was observed between longer Tmax and the presence of bulky disease or higher FLIPI risk category. However, there was no or small (1 day) differences in median Tmax.

Pharmacodynamics

Results in the 2L+ group are highlighted for pharmacodynamic parameters as this group was evaluated for pharmacodynamic-safety relationships.

Overall, pharmacodynamic trends were similar across the 4L+, 3L, 3L+, 2L, and 2L+ groups.

In the 2L+ group, an increase in the proportion of subjects with B-cell aplasia was observed from 76.7% of subjects at baseline to 99.2% of subjects by Day 8, with B-cell aplasia maintained in the majority of subjects (56.9%) who reached Day 545 (18 months).

Pharmacokinetics-Efficacy/Safety Relationships

The 2L+ and 3L+ groups were used for assessment of PK-efficacy relationships, while the 2L+ group was used for assessment of PK-safety relationships.

In the 2L+ group, a potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and longer PFS, DOR and DOR if BOR is CR per FDA algorithm (definition of FDA algorithm is provided in Section 8.1.1). No apparent relationship was observed between transgene PK parameters and CR. The relationships between transgene PK parameters and response (BOR of either CR or PR) were not assessed because the number of evaluable non-responders was less than 5. Similar PK-efficacy relationships were observed in the 3L+ group.

In the 2L+ group, a potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher incidence of any-grade CRS and any-grade iiNT. A potential relationship was also observed between earlier transgene Tmax and higher incidence of any-grade CRS and any-grade iiNT, however, the difference in median Tmax was small (0.5 days and 1.5 days, respectively). The relationship

between PK parameters and Grade ≥ 3 CRS or Grade ≥ 3 iiNT was not assessed because the number of evaluable subjects with Grade ≥ 3 CRS and Grade ≥ 3 iiNT was less than 5 (N = 1 and N = 3, respectively).

Pharmacodynamic-Safety Relationships

The 2L+ group (Total Cohorts 1, 2, 3) was used for assessment of pharmacodynamic-safety relationships.

No baseline soluble biomarker, CRP, or ferritin median levels demonstrated an association comparing any-grade CRS versus no CRS or any-grade iiNT versus no iiNT categories. Among the soluble biomarkers, peak levels of TARC, GM-CSF, and IL-6 were associated with any-grade CRS versus no CRS, as was peak CRP. None of the soluble biomarkers, CRP, or ferritin at peak levels were associated with any any-grade iiNT versus no iiNT.

Immunogenicity

In the 2L+ group, the incidence of ATA was 22.3% (27 of 121 subjects); the prevalence of ATA was 1.6% (2 of 123 subjects). No subjects had treatment-boosted ATA. There were no clear differences in efficacy (ORR and CRR in the 3L+ and 2L+ groups), safety (the incidence of any-grade CRS, Grade ≥ 3 CRS, any-grade iiNT, and Grade ≥ 3 iiNT in the 2L+ group), and PK (transgene Cmax and AUC[0-28] in the 2L+ group) between subjects who had treatment-induced ATA and subjects who did not have treatment induced or treatment-boosted ATA.

Confirmation of the selected Doses and Regimens in Study FOL-001

The drug product consists of 2 separate, autologous cellular components: a cryopreserved CD8+ T cell suspension and a cryopreserved CD4+ T cell suspension for IV administration that are infused at the 1:1 ratio of each cellular component. Each component comprises of pure CD8+ or CD4+ T cells that express CD19-specific CAR. The CD19-specific CAR comprises a single chain fragment variable binding domain derived from a murine CD19-specific monoclonal antibody (FMC63) and the 4-1BB and CD3ζ chain signaling domains. Each component is an individual suspension of cells formulated in a cryopreservation medium, filled into cryogenic vials composed of cyclic olefin copolymer (4 vials, each filled at 5 mL with 4.6 mL extractable volume per vial).

Clinical efficacy and safety results: In FOL-001, liso-cel dose of 100 × 10^6 CAR+ T cells demonstrated clinically meaningful efficacy in subjects with R/R FL with high ORR, CRR, and durable responses. The median number of total (CD8+ and CD4+) liso-cel administered dose cell counts for 3L+ and 2L groups were 100.02 × 10^6 CAR+ T cells (range: 93.4 × 10^6 to 109.2 × 10^6) and 99.92 × 10^6 CAR+ T cells (range: 97.4 × 10^6 to 102.9 × 10^6), respectively, which were within the proposed liso-cel dose range of 90 to 110 × 10^6 CAR+ T cells. The overall safety profile of a liso-cel in R/R FL was manageable and consistent with what previously observed in the marketed indication of R/R LBCL, with no new safety concerns.

Although the planned dose was 100 × 10^6 CAR+ T cells, a dose range of 90 - 110 × 10^6 CAR+ T cells (100 × 10^6 +/- 10%) was assessed to be acceptable for approval given the

variability in manufacturing of a biological product, and data to support efficacy at doses lower than 100 × 10^6 and safety data with doses up to 110 × 10^6.

PK/Pharmacodynamic: A similar PK and pharmacodynamic profile was observed across the 4L+, 3L, 3L+, 2L, and 2L+ groups in Study FOL-001.

Exposure-Response efficacy and safety analysis: The benefit -risk profile is not expected to be impacted by liso-cel at the proposed dose range of 90 to 110 × 10^6.

The FDA's Assessment:

Please refer to the FDA clinical pharmacology review memo for the further discussion of this section.

Table 4 shows the doses of CD4 and CD8 components administered to 3L+ FL patients.

Table 4. FDA Analysis of Dose of Liso-cel Administered to 3L+ FL Subjects in Study FOL-001

N=107	Total	CD4	CD8
Median (x10^6 CAR+ T cells)	100.02	49.99	49.82
Range (x10^6 CAR+ T cells)	93.4 to 109.2	43.14 to 58.80	42.29 to 51.71

Source: FDA Analysis of ADEX dataset from Study FOL-001
Abbreviations: FL, follicular lymphoma

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

Table 5: Applicant - Clinical Studies Relevant to this sBLA

Study	Study Design	Study Population	No. CAR+ T cells	Study Status Data Cutoff Date Number of Liso-cel-Treated Subjects	Indications
JCAR017-FOL-001 (TRANSCEND FL) Regions: US, Europe, Japan, Canada	Phase 2, Open-label, single-arm, multicohort, liso-cel monotherapy	Adult 2L+ iNHL (2L+ FL Grade 1, 2, or 3A and 3L+ MZL)	100 × 10^6	Ongoing 27-Jan-2023 130 (FL) 48 (MZL)	2L+ FL 3L+ MZL

Table 5: Applicant - Clinical Studies Relevant to this sBLA

Study	Study Design	Study Population	No. CAR+ T cells	Study Status Data Cutoff Date Number of Liso-cel-Treated Subjects	Indications
GC-LTFU-001 non-interventional Regions: US, Europe, Japan	Non-interventional multi-site	All subjects treated with a Sponsor CAR+ T cell therapy, including liso-cel	NA	Ongoing 31-Jan-2023 205[a]	

[a] As of the data cutoff date, Study GC-LTFU-001 enrolled the following monotherapy liso-cel-treated subjects: 19 from 017004, 22 from BCM-001, 25 from 017007, 1 from FOL-001, and 16 from 017001 MCL. For the following studies, GC-LTFU-001 enrolled: 87 subjects from 017001 DLBCL, 18 from BCM-003 Arm B, and 17 from 017006; however, for these 3 studies, no LTFU data was integrated with parent studies.

The FDA's Assessment:

FDA agrees with the Applicant's description of clinical studies. Study FOL-001 is the primary study in support of this Biologics License Application (BLA).

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study FOL-001

Trial Design

The Applicant's Description:
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 (Figure 1 and Table 6).

Results provided in this document cover only subjects with FL; those from subjects with MZL will be provided in subsequent submission.

Figure 1: Applicant - Study FOL-001 Study Design

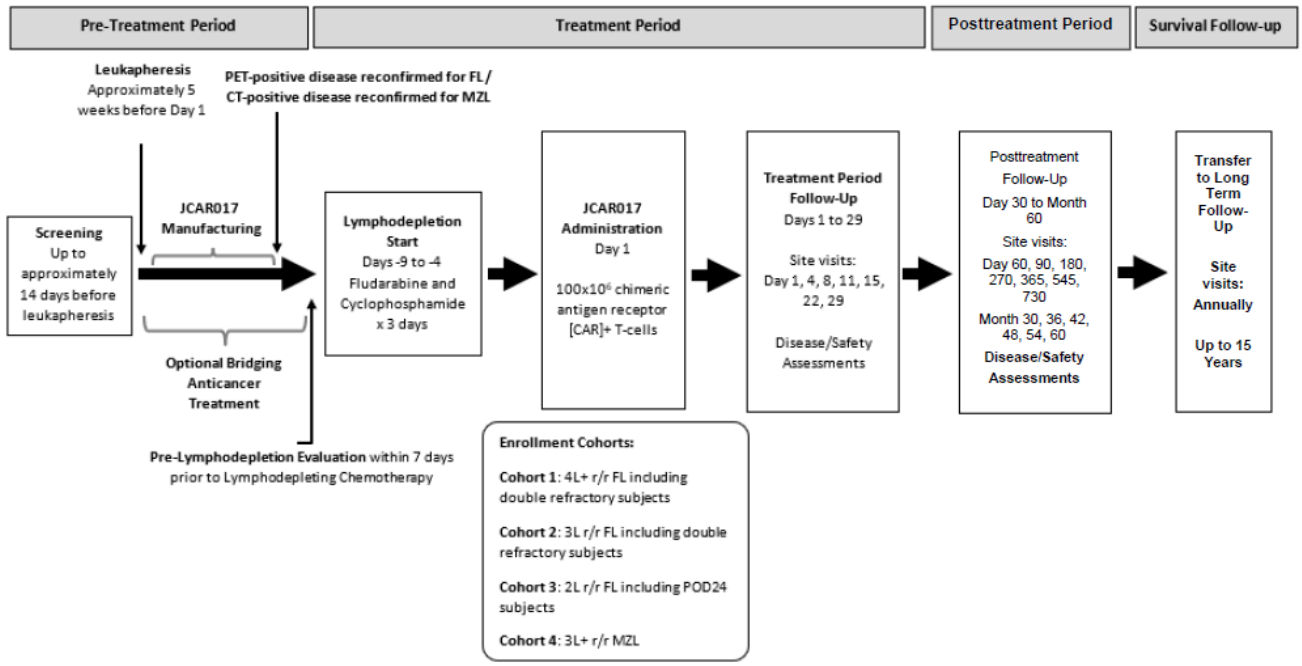


Table 6: Applicant - Study FOL-001 Study Design

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.[51] 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.

Table 6: Applicant - Study FOL-001 Study Design

	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,[51] 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.
Study Status	First subject first visit: 14-Jul-2020. Study ongoing.

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. After reviewing baseline demographics and clinical characteristics of the trial population (Table 13) and comparing to the overall R/R FL population in the US, the trial participants adequately represent the overall US R/R FL population.

An IRC was established to review data related to disease response assessments during the study and determine remission and relapse for the primary analysis and secondary analyses.

The FDA's Assessment:

FDA agrees with the Applicant's description of JCAR017-FOL-001 (TRANSCEND FL) study.

Study Endpoints

The Applicant's Description:

Table 7: Applicant - Study FOL-001 Endpoints

Endpoint	Endpoint Description
Primary Endpoint	
ORR as assessed by PET-CT (for FL) or CT (for MZL)[a] using "The Lugano Classification."[b]	Percentage of subjects achieving a response (CR or PR) at any time up to 60 months after liso-cel treatment (EOS)
Secondary Endpoints	
CRR as assessed by PET-CT (for FL) or CT (for MZL)[a] using "The Lugano Classification."[b]	Percentage of subjects achieving a CR at any time up to 60 months after liso-cel treatment (EOS)
DOR as assessed by PET-CT and/or CT using "The Lugano Classification.[b]	Time from first response (CR or PR) to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel treatment (EOS)
DOR if BOR is CR, as assessed by PET-CT and/or CT[c] using "The Lugano Classification."[b]	For subjects with a BOR of CR, time from first response (CR or PR) to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel treatment (EOS)[d]
PFS as assessed by PET-CT and/or CT using "The Lugano Classification."[b]	Time from start of liso-cel to disease progression or death from any cause, whichever occurs first up to 60 months after liso-cel treatment (EOS)
OS	Time from start of liso-cel to time of death due to any cause up to 60 months after liso-cel treatment (EOS)
Safety	Type, frequency, and severity of AEs and laboratory abnormalities up to 60 months after liso-cel treatment (EOS)
PK	Cmax, Tmax, AUC, and persistence of liso-cel as assessed by PCR up to 60 months after liso-cel treatment (EOS)
HRQoL	HRQoL primary domains of interest assessed by EORTC QLQ-C30 (global health/QoL, physical functioning, cognitive functioning, fatigue, pain) and FACT-LymS up to 24 months after liso-cel treatment
Exploratory Endpoints	
Immunogenicity	Humoral immune response ATA up to 24 months after liso-cel treatment
Peripheral Biomarker[e]	• Immune cell subsets and gene expression analysis up to 24 months after liso-cel treatment • cfDNA/MRD up to 60 months after liso-cel treatment (EOS)
Pharmacodynamic Biomarkers	Measurement of peripheral B-cell aplasia and soluble factors up to 60 months after liso-cel treatment (EOS)
Tumor Biomarker	Cellular and molecular profiling of tumor tissue to explore potential efficacy and resistance mechanisms up to 60 months after liso-cel treatment (EOS)

Table 7: Applicant - Study FOL-001 Endpoints

Endpoint	Endpoint Description
HRQoL	HRQoL parameters assessed by the remaining subscales of: EORTC QLQ-C30, up to 24 months after liso-cel treatment
Health Utility and Global Health Assessment	EQ-5D-5L health utility and VAS scores up to 60 months after liso-cel treatment (EOS)
Hospital Resource Utilization	Number of inpatient, ICU days and outpatient visits up to 60 months after liso-cel treatment (EOS)
COVID-19 Serology Status	Exploratory measurements of COVID-19 serology (anti-COVID-19 total or IgG), and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarker findings up to 60 months after liso-cel treatment (EOS).

[a] MZL has lower FDG avidity compared to FL.[52]
[b] Per Study FOL-001 protocol, PET scan was used to evaluate bone marrow lymphoma involvement per a modified Lugano Classification.[51]
[c] PET/CT is not required for subjects that reach a PET/CT CR and these subjects may subsequently be monitored by CT only.
[d] Of note, per SAP, DOR if BOR is CR defined as the time from first complete response to disease progression or death from any cause up to 60 months after liso-cel infusion.
[e] All peripheral biomarkers were collected up until 24 months with the exception of cfDNA, which was collected up until 60 months (EOS).

The FDA's Assessment:

The FDA's assessment for efficacy was based on the primary endpoint of ORR defined as percentage of patients with best overall response (BOR) of CR or PR, as confirmed by IRC per 2014 Lugano classification (Cheson et al. 2014), further supported by DOR. The time to event endpoints, including PFS and OS from a single arm trial, are not interpretable and are considered exploratory.

The IRC charter of Study FOL-001 assessed response evaluation using a modified Lugano classification (Cheson et al. 2014). It should be noted that the modified Lugano is created by this Applicant for the purpose of clinical trials of liso-cel, including FOL-001 Study, and is not a validated or published response criteria for lymphoma. Modified Lugano Criteria in Study FOL-001 protocol outlines following key modifications to Lugano 2014 criteria:

1) It primarily utilizes positron emission tomography (PET) computerized tomography (CT) for response classification in FL.
2) At screening, PET scan is used to assess bone marrow (BM) involvement without requirement of BM biopsy.
3) Post infusion, assessment of BM involvement is by PET CT and will additionally require BM biopsy for confirmation of a CR.
4) PET CT is not required once a subject achieves a CR unless a progressive disease (PD) is suspected on a follow up CT/magnetic resonance imaging.

5) Censoring for DOR and PFS is done as per European Medicines Agency censoring rules. (see Appendix 17.3)

During prior meeting (CRMTS #13766), the FDA had communicated concerns with the Applicant's proposal to use modified Lugano criteria (Cheson et al. 2014), and reiterated following:

1) IRC-assessed ORR using 2014 Lugano criteria will be an acceptable primary endpoint for FL.
2) The acceptability of using a PET prioritized response criteria for primary analysis will be contingent on proportion of subjects having PET performed.
3) 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 BM. Thus, subjects who are deemed to have a CR to therapy by imaging criteria must have a BM examination documenting absence of disease to be considered a CR if baseline BM was positive, indeterminate, or unknown for lymphoma involvement. Without this confirmatory BM biopsy, CR should be downgraded to PR. The Agency's primary efficacy analysis and the regulatory decision will follow the 2014 Lugano criteria.
4) Clinical findings of progression (not radiographically confirmed) should be incorporated in the final adjudication of response by the oncologist.
5) Recommendation to use FDA censoring rules for analysis of DOR and PFS (see Appendix 17.2 and 17.3)

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample size: Assuming a 20% dropout rate, approximately 213 subjects were to be enrolled to ensure that approximately 50 subjects in Cohort 1, 40 subjects in Cohort 2, 20 subjects in Cohort 3, and 60 subjects in Cohort 4 were treated with liso-cel.

Efficacy analyses were performed on the Liso-cel-treated Efficacy Analysis Set of Cohorts 1, 2, and 3. Select efficacy analyses (ORR, CRR, DOR, PFS and OS) were also performed based on the Leukapheresed (ITT) Analysis Set and Liso-cel-treated Analysis Set.

Primary endpoint was ORR, defined as the percentage of subjects with a BOR of CR or PR up to 60 months after liso-cel infusion as determined by an IRC. The primary efficacy analyses were based on the Liso-cel-treated Efficacy Analysis Set per IRC charter based on a modified Lugano Classification[51] using PET/CT scans for disease assessments, including assessment of lymphomatous bone marrow involvement via PET.

The efficacy analysis for 4L+ and 3L+ R/R FL groups was planned for when the approximate number of planned treated subjects in both groups was followed for DOR for approximately 12 months after first response of CR or PR per the Investigator's assessment or until death, disease progression, or withdrawal from the study. The approximate number of treated subjects was 50 for the 4L+ R/R FL group and 90 for the 3L+ R/R FL group.

The efficacy analysis of 2L R/R FL group was planned when the approximate number of planned treated subjects was followed for DOR for approximately 12 months after first response of CR or PR per the Investigator's assessment or until death, disease progression, or withdrawal from the study. The approximate number of treated subjects for the 2L R/R FL group was 20.

Key secondary endpoints of CRR, DOR, and PFS were all assessed by PET-CT based on a modified Lugano Classification.[51] DOR, PFS, and OS were summarized using the KM method and corresponding KM curves were plotted. Medians, ranges, and corresponding 95% CIs for median were presented. DOR and PFS analyses were conducted using EMA censoring rules. The OS analysis was planned to include all available survival information with long-term follow-up data.

Sensitivity analyses of primary and secondary efficacy endpoints were performed:

- Per FDA algorithm, based on the IRC Procedures Document, according to the Lugano Classification,[51] with a negative BMB required to confirm CR otherwise time point assessment with CMR on PET downgraded to PR, and the finding of CMR, PMR, SD on PET scan considered PD if there was evidence of progression on CT at a time point; for the analysis of DOR and PFS, FDA censoring rules are applied (Table 8).
- Per the response assessed by the Investigator.
- In the Leukapheresed (ITT) Set. A subject in the Leukapheresed (ITT) Set who did not receive cell product was considered not evaluable (ie, a non-responder) for the sensitivity analyses of ORR and CR rate. For the Leukapheresed (ITT) Set, PFS was defined as the time from leukapheresis to PD or death from any cause, whichever occurred first up to 60 months after infusion and OS was defined as the time from leukapheresis to time of death due to any cause up to 60 months after infusion.

In this Assessment Aid, efficacy analyses are presented per the FDA algorithm only (definitions summarized in Table 8). Efficacy analyses per the FDA Algorithm and IRC charter are presented in SCE and clinical overview.

Table 8: Applicant - Definitions of FDA Algorithm and IRC Charter

Terminology	FDA algorithm	IRC charter
Response evaluation	IRC Procedures Document using the Lugano Classification	IRC charter using a modified Lugano Classification
Censoring rules	FDA censoring rules for DOR and PFS	EMA censoring rules for DOR and PFS
Per-protocol analyses	Sensitivity analyses; referred as "FDA criteria" in the statistical outputs	Primary analyses; referred as "IRC assessment" in the statistical outputs

Subgroup analyses were performed based on demographic variables from the subject's baseline status, such as age, sex, ethnicity, race, anticancer treatment for disease control (yes vs no), received concomitant GCSF (yes vs no). Subgroup analyses were performed by cohort for the primary and secondary efficacy endpoints: ORR, CRR, DOR, PFS, and OS.

The FDA's Assessment:

FDA's primary efficacy analysis was performed on a total of 94 subjects from cohorts 1 and 2 of JCAR017-FOL-001 Study who had relapsed or refractory FL after 2 or more prior lines of therapy, evidence of PET-positive and measurable disease at baseline as per Lugano 2014 criteria (Cheson et al. 2014), were treated with conforming liso-cel at intended dose (90 to 110 x 10^6 CAR positive T cells), and had a minimum of 9 months follow-up for DOR as per IRC. Additionally, efficacy analysis was conducted on intention-to- treat population (i.e., all leukapheresed patients).

Protocol Amendments

The Applicant's Description:
Key study level changes to Study FOL-001 after the original protocol are provided below and in Table 9.

The primary endpoint was changed from CRR to ORR and secondary endpoint from ORR to CRR in Protocol Amendment 1.0 (06-Jul-2021), while the study was ongoing. Since ORR has been traditionally used as an endpoint in indolent NHL trials, changing the primary endpoint from CRR to ORR allowed a more relevant comparison to real world data, as well as prior indolent NHL trials. The interpretation of ORR generally remains consistent across response criteria, while different versions of response criteria are used to define CRR in clinical trials. Importantly, this decision was not influenced by Study FOL-001 trial data, as no efficacy analyses based on IRC data had been conducted before the protocol amendment.

To satisfy FDA requests, sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CRR, DOR, and PFS, based on the description in the IRC Procedures Document and the application of FDA censoring rules for DOR and PFS (analyses "per FDA algorithm") were added to the SAP.

Table 9: Applicant - Summary of Key Changes to Protocol Study FOL-001

Document (Amendment) /Date	Summary of Key Changes	Planned Sample Size	Subjects Enrolled at time of Protocol Amendment
Protocol Amendment 1.0 / 06-Jul-2021	• Changed primary endpoint from CRR to ORR and secondary endpoint from ORR to CRR • Added requirement for BMB to confirm all CMRs in FL subjects as part of a sensitivity analysis • Broadened third line population from 'high risk' to 'all comers' given that for FL patients in the third line of therapy the five-year survival rate is only 20%, highlighting the urgent need for treatment of the 'all comers' population. This led to a 3L+ 'all comers' analysis. Updated hierarchical testing to 3L+ and then conducting 4L+ analysis. • Increased the number of subjects enrolled in the 4L+ cohort and decreased the number of subjects enrolled in the 3L cohort • Added requirement of upper gastrointestinal endoscopy/biopsy for subjects with gastric MALT lymphoma	188	116
Protocol Amendment 2.0 / 10-Jul-2022	• The posttreatment follow-up period was extended from 2 years (24 months) to 5 years (60 months); assessment planning updated accordingly • Extended timing for statistical analyses • Added new assessment for PD/relapse: local results on target antigen expression if available (ie, CD19 expression in subjects who received prior CD19-directed therapy) • Increased total number of subjects from approximately 188 to approximately 213	213	181

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments.

8.1.2 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with GCP, as defined by the ICH and in accordance with the ethical principles underlying EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The protocol, amendments, and subject informed consent received appropriate approval by the IRB/IRC prior to initiation of study at the site. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided in the study report. The quality of data collected and analyzed was monitored according

to BMS standard operating procedures.

There were no GCP deviations impacting the study, and no sites were closed for GCP issues. No serious breaches were reported.

The FDA's Assessment:

FDA agrees with the Applicant's description. A statement indicating compliance with GCP was provided in the application. No concerns were identified during the clinical site inspections.

Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 17.2). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the FOL-001 clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:

See Appendix 17.5.

Patient Disposition

Data:

Table 10: Applicant - Analysis Populations - Screened Set

Analysis Population	4L+ FL	3L FL	3L+ FL	2L FL	2L+ FL	Total
Screened Set[a]						154
Eligible Set[b]						139
Leukapheresed (ITT) Set[c]	65 (100.0)	49 (100.0)	114 (100.0)	25 (100.0)	139 (100.0)	139 (100.0)
Liso-cel-treated Set[d]	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)	130 (93.5)
Liso-cel-treated Efficacy Set[e]	53 (81.5)	48 (98.0)	101 (88.6)	23 (92.0)	124 (89.2)	124 (89.2)
Outpatient Analysis Set[f]	12 (18.5)	2 (4.1)	14 (12.3)	1 (4.0)	15 (10.8)	15 (10.8)
PK Analysis Set[g]	59 (90.8)	48 (98.0)	107 (93.9)	23 (92.0)	130 (93.5)	130 (93.5)
PK Evaluable Analysis Set[h]	59 (90.8)	46 (93.9)	105 (92.1)	23 (92.0)	128 (92.1)	128 (92.1)

Table 10: Applicant - Analysis Populations - Screened Set

Analysis Population	4L+ FL	3L FL	3L+ FL	2L FL	2L+ FL	Total
PRO Analysis Set[i]	56 (86.2)	46 (93.9)	102 (89.5)	20 (80.0)	122 (87.8)	122 (87.8)

Percentages are based on number of Leukapheresed Set.

[a] Subjects signed informed consent.
[b] Subjects signed consent who meet all inclusion/exclusion criteria.
[c] Subjects signed consent who undergo leukapheresis and meet all inclusion/exclusion criteria.
[d] Subjects received a dose of conforming liso-cel.
[e] Subjects received a dose of liso-cel with PET positive disease present before liso-cel administration per IRC. Subjects without baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration were excluded.
[f] Subjects monitored as an outpatient in liso-cel-treated set.
[g] Subjects with any available PK measurements by PCR in the liso-cel-treated set.
[h] Subjects with at least one evaluable PK parameter in the liso-cel-treated set.
[i] Subjects completed pre-LDC PRO questionnaires and with at least one post-baseline measurement in the liso-cel-treated set.

Source: ADSL

Table 11: Applicant - Key Dates and Follow-up - Study FOL-001

First Subject First Visit	14-Jul-2020
First FL Subject Enrolled (Day of Leukapheresis)	29-Jul-2020
Last FL Subject Enrolled (and Treated)	10-Feb-2022 (04-Apr-2022)
Clinical Data Cutoff	27-Jan-2023
Database Lock	31-Mar-2023
Median on-study follow-up, months (range: min, max)[a]	18.89 (0.3, 28.2)

[a] Study follow-up time is defined in months as: (EOS date - date of liso-cel infusion + 1)/ 30.4375. For subjects continuing on-study follow-up time is defined as: (data cutoff date - date of liso-cel infusion + 1) / 30.4375.

Table 12: Applicant - Subject Disposition - Liso-cel-treated Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Subjects Received Liso-cel	59 (100.0)	48 (100.0)	107 (100.0)	23 (100.0)	130 (100.0)
Subjects Ongoing on Treatment Period	0	0	0	0	0
Subjects Completed Treatment Period	59 (100.0)	47 (97.9)	106 (99.1)	22 (95.7)	128 (98.5)
Subjects Discontinued Treatment Period	0	1 (2.1)	1 (0.9)	1 (4.3)	2 (1.5)

Table 12: Applicant - Subject Disposition - Liso-cel-treated Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Primary Reason for Treatment Period Discontinuation					
Adverse Event	0	0	0	1 (4.3)	1 (0.8)
Withdrawal by Subject	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subjects Continued to Posttreatment Follow-Up Period	59 (100.0)	47 (97.9)	106 (99.1)	22 (95.7)	128 (98.5)
Subjects Ongoing on Posttreatment Follow-Up Period	51 (86.4)	42 (87.5)	93 (86.9)	22 (95.7)	115 (88.5)
Subjects Completed Posttreatment Follow-Up Period[a]	0	0	0	0	0
Subjects Discontinued Posttreatment Follow-Up Period	8 (13.6)	5 (10.4)	13 (12.1)	0	13 (10.0)
Primary Reason for Discontinuing Posttreatment Follow-Up Period					
Death	5 (8.5)	2 (4.2)	7 (6.5)	0	7 (5.4)
Withdrawal by Subject	2 (3.4)	2 (4.2)	4 (3.7)	0	4 (3.1)
Physician Decision	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Other	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Discontinued Posttreatment Follow-Up Period Due to Covid-19 Pandemic	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subjects Continued to Long-Term Follow-Up Protocol[b]					
Yes	1 (1.7)	0	1 (0.9)	0	1 (0.8)
No	7 (11.9)	6 (12.5)	13 (12.1)	1 (4.3)	14 (10.8)
Reason Subject Did Not Continue to Long-Term Follow-Up Protocol					
Death	5 (8.5)	3 (6.3)	8 (7.5)	1 (4.3)	9 (6.9)
Progressive Disease	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Withdrawal by Subject	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Subject Refused	0	1 (2.1)	1 (0.9)	0	1 (0.8)

Table 12: Applicant - Subject Disposition - Liso-cel-treated Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Withdrawal by Subject After Initial Consent	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Other	1 (1.7)	0	1 (0.9)	0	1 (0.8)

Treatment period is defined as the initiation of lymphodepleting chemotherapy and concludes at Day 29 after liso-cel infusion. Posttreatment follow-up period is defined as the period starting on Day 30 post-liso-cel visit and ending at the 60-month post-liso-cel visit.

[a] Includes subjects that completed the posttreatment follow-up period based on the prior protocol that only required 2 years.

[b] Per protocol, all subjects who either complete the follow-up period specified in the protocol or prematurely withdraw after liso-cel infusion, would be eligible to enroll in the LTFU study (to be continued for up to 15 years after the infusion of liso-cel) at the end of study visit or at the time of withdrawal, respectively; a separate ICF was to be provided for the LTFU study.

Source: ADSL

The Applicant's Position:

The Liso-cel-treated Efficacy Analysis Set was the primary population used for the efficacy analyses and the Liso-cel-treated Analysis Set was the primary population used for the safety analyses (Table 10).

The majority of screened subjects (139/154; 90.3%) were leukapheresed. Of the 139 leukapheresed subjects, 137 (98.6%) subjects entered the treatment period, and 130 (93.5%) subjects were infused with liso-cel across 3 FL cohorts (ADSL).

As of the clinical data cutoff date, all FL cohorts (Cohorts 1, 2, and 3) had completed enrollment (Table 11), and enrollment was continuing for MZL subjects in Cohort 4.

Most subjects completed the treatment period (Days 1 to 29) in both 3L+ (99.1%) and 2L (95.7%) and continued to posttreatment follow-up period (Day 30 to Month 60). Most subjects from 3L+ group (86.9%) and all subjects from 2L group were ongoing in the posttreatment follow-up period at the data cutoff date (Table 12).

The FDA's Assessment:

A total of 154 subjects with FL were enrolled in Study JCAR-FOL-001; 139 underwent leukapheresis. A total of 130 subjects were treated with liso-cel, including 124 subjects treated with conforming product; 101 of those subjects had received 2 or more prior lines of therapy, whereas 23 had received 1 prior line. Out of 101 subjects in 3L+FL, 94 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 (Cheson et al. 2014), received one dose of conforming liso-cel, and had a minimum of 9 months of follow-up for DOR. Out of those 101 patients, 7 were excluded from FDA's primary efficacy evaluable population since they did not have a minimum of 9 months of DOR follow up.

Additionally, efficacy was analyzed on 23 FL patients with 1 prior line of therapy.

Protocol Violations/Deviations

The Applicant's Position:
Important Protocol Deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

As of the clinical cutoff (27-Jan-2023), the majority of Important Protocol Deviations were due to procedures/tests (2 [1.4%] subjects) (ADSL, ADPD).

23 COVID-19 related protocol deviations were captured prior to the clinical cutoff date. None of these protocol deviations had an impact on the quality of the data in this study (ADSL, ADPD).

The FDA's Assessment:

Based on FDA analysis, important protocol deviations occurred in three subjects; in two subjects, baseline PET-CT scans were done prior to the completion of bridging chemotherapy. Neither of these subjects were included in the JCAR017-FOL-001 efficacy population. The third subject was missing supportive data for evidence of FL within 6 months of screening.

Table of Demographic Characteristics

Data:

Table 13: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Age (Years)					
N	59	48	107	23	130
Median	64.0	60.0	62.0	53.0	60.0
Q1, Q3	56.0, 70.0	53.5, 67.0	55.0, 69.0	42.0, 62.0	53.0, 68.0
Min, Max	23, 80	27, 78	23, 80	34, 69	23, 80
Age group (Years) - n (%)					
< 65	34 (57.6)	31 (64.6)	65 (60.7)	18 (78.3)	83 (63.8)
≥ 65 - < 75	18 (30.5)	14 (29.2)	32 (29.9)	5 (21.7)	37 (28.5)
≥ 75	7 (11.9)	3 (6.3)	10 (9.3)	0	10 (7.7)
Sex - n (%)					
Female	24 (40.7)	17 (35.4)	41 (38.3)	6 (26.1)	47 (36.2)
Male	35 (59.3)	31 (64.6)	66 (61.7)	17 (73.9)	83 (63.8)
Ethnicity - n (%)[a]					
Hispanic or Latino	4 (6.8)	1 (2.1)	5 (4.7)	1 (4.3)	6 (4.6)
Not Hispanic or Latino	39 (66.1)	35 (72.9)	74 (69.2)	15 (65.2)	89 (68.5)
Not reported	16 (27.1)	12 (25.0)	28 (26.2)	7 (30.4)	35 (26.9)

Table 13: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Primary race - n (%)[b]					
Asian	7 (11.9)	3 (6.3)	10 (9.3)	2 (8.7)	12 (9.2)
Black or African American	3 (5.1)	0	3 (2.8)	1 (4.3)	4 (3.1)
White	31 (52.5)	29 (60.4)	60 (56.1)	9 (39.1)	69 (53.1)
Not collected or unknown	18 (30.5)	16 (33.3)	34 (31.8)	11 (47.8)	45 (34.6)
Region - n (%)					
Europe	27 (45.8)	34 (70.8)	61 (57.0)	12 (52.2)	73 (56.2)
Japan	6 (10.2)	3 (6.3)	9 (8.4)	1 (4.3)	10 (7.7)
North America	26 (44.1)	11 (22.9)	37 (34.6)	10 (43.5)	47 (36.2)
Type of lymphoma and histological subtype/grade at screening - n (%)					
Grade 1	3 (5.1)	6 (12.5)	9 (8.4)	6 (26.1)	15 (11.5)
Grade 2	41 (69.5)	31 (64.6)	72 (67.3)	11 (47.8)	83 (63.8)
Grade 3A	15 (25.4)	10 (20.8)	25 (23.4)	6 (26.1)	31 (23.8)
Unknown	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Time from initial B-NHL diagnosis to liso-cel infusion (years)					
N	59	48	107	23	130
Median	7.288	4.62	5.136	1.993	4.709
Q1, Q3	4.164, 12.134	2.509, 6.341	3.370, 8.794	1.131, 4.394	2.968, 7.860
Min, Max	1.87, 35.27	0.70, 18.74	0.70, 35.27	0.76, 11.38	0.70, 35.27
Time from completion of most recent systemic regimen to progression (month)					
N	58	46	104	23	127
Within ≥ 0 - ≤ 6 months - n (%)	31 (52.5)	18 (37.5)	49 (45.8)	11 (47.8)	60 (46.2)
Within > 6 - ≤ 12 months - n (%)	5 (8.5)	7 (14.6)	12 (11.2)	2 (8.7)	14 (10.8)
Patients progressed before regimen completion - n (%)	13 (22.0)	7 (14.6)	20 (18.7)	4 (17.4)	24 (18.5)
FL international prognostic index (FLIPI) at screening - n (%)					
Low risk (0-1)	9 (15.3)	3 (6.3)	12 (11.2)	11 (47.8)	23 (17.7)
Intermediate risk (2)	14 (23.7)	20 (41.7)	34 (31.8)	4 (17.4)	38 (29.2)
High risk (3-5)	36 (61.0)	25 (52.1)	61 (57.0)	8 (34.8)	69 (53.1)
Ann Arbor stage at screening - n (%)					
Stage I	1 (1.7)	0	1 (0.9)	1 (4.3)	2 (1.5)
Stage II	4 (6.8)	7 (14.6)	11 (10.3)	5 (21.7)	16 (12.3)
Stage III	18 (30.5)	21 (43.8)	39 (36.4)	6 (26.1)	45 (34.6)
Stage IV	36 (61.0)	20 (41.7)	56 (52.3)	11 (47.8)	67 (51.5)
ECOG performance status at screening - n (%)					
0	30 (50.8)	35 (72.9)	65 (60.7)	17 (73.9)	82 (63.1)
1	29 (49.2)	13 (27.1)	42 (39.3)	6 (26.1)	48 (36.9)
ECOG performance status pre-liso-cel infusion - n (%)					
0	24 (40.7)	28 (58.3)	52 (48.6)	16 (69.6)	68 (52.3)
1	33 (55.9)	17 (35.4)	50 (46.7)	7 (30.4)	57 (43.8)
2	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Not reported	1 (1.7)	3 (6.3)	4 (3.7)	0	4 (3.1)
Modified GELF criteria met at time of most recent relapse - n (%)					
Yes	31 (52.5)	26 (54.2)	57 (53.3)	16 (69.6)	73 (56.2)

Table 13: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Symptoms attributable to FL	8 (13.6)	5 (10.4)	13 (12.1)	6 (26.1)	19 (14.6)
Threatened end-organ function/ cytopenia secondary to lymphoma /bulky disease	12 (20.3)	12 (25.0)	24 (22.4)	7 (30.4)	31 (23.8)
Splenomegaly	1 (1.7)	3 (6.3)	4 (3.7)	0	4 (3.1)
Steady progression over at least 6 months	10 (16.9)	6 (12.5)	16 (15.0)	3 (13.0)	19 (14.6)
No	28 (47.5)	22 (45.8)	50 (46.7)	7 (30.4)	57 (43.8)
Double refractory status per protocol[c] - n (%)					
Yes	36 (61.0)	33 (68.8)	69 (64.5)	11 (47.8)	80 (61.5)
No	23 (39.0)	15 (31.3)	38 (35.5)	12 (52.2)	50 (38.5)
POD24 status per protocol[d] - n (%)					
Yes	21 (35.6)	25 (52.1)	46 (43.0)	12 (52.2)	58 (44.6)
No	38 (64.4)	23 (47.9)	61 (57.0)	11 (47.8)	72 (55.4)
POD24 of 1st line therapy with anti-CD20 and alkylator[e]- n (%)					
Yes	27 (45.8)	31 (64.6)	58 (54.2)	15 (65.2)	73 (56.2)
No	32 (54.2)	16 (33.3)	48 (44.9)	8 (34.8)	56 (43.1)
Not estimable	0	1 (2.1)	1 (0.9)	0	1 (0.8)
Refractory to last line of therapy per protocol - n (%)[f]					
Yes	24 (40.7)	14 (29.2)	38 (35.5)	3 (13.0)	41 (31.5)
No	35 (59.3)	34 (70.8)	69 (64.5)	20 (87.0)	89 (68.5)

Baseline characteristic is defined as the latest measurement on or prior to the date of liso-cel infusion.

[a] Ethnicity "Not reported" is auto populated due to local privacy regulations for France, Germany, Sweden, United Kingdom.

[b] Race "Not Collected or Unknown" is auto populated due to local privacy concerns for France, Germany, Sweden, United Kingdom.

[c] Double refractory status can be met at any line of therapy that includes an anti-CD20 antibody and alkylating agent.

Definition per protocol: double refractory subjects are those who are refractory to both an anti-CD20 antibody and an alkylating agent (defined as subjects who did not respond or progressed during or up to 6 months after completing treatment with an anti-CD20 monoclonal antibody and an alkylating agent) or refractory to anti-CD20 maintenance therapy (defined as subjects who did not respond or progressed during or up to 6 months after completing maintenance treatment with an anti-CD20 monoclonal antibody).

[d] Definition of POD-24 per protocol. As per protocol and CRF, progression of disease within 24 months of diagnosis after initiating treatment with an anti-CD20 and alkylating agent within the first 6 months of initial FL diagnosis.

[e] POD24 definition: Progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent.

[f] Definition per protocol: refractory lymphoma is defined as a best response of SD or PD after prior therapy (irrespective of time interval).

Refractory is defined as subjects that had progression while receiving their last line of systemic therapy or within 6 months of completing their last line of therapy can be calculated from variable “patients progressed before regimen completion” and patients that progressed “within > 0 - < 6 months from completion of most recent systemic regimen”, ie, for 2L+ 64.6% (84/130).

Source: ADSL, ADDX

The Applicant's Position:
In the Liso-cel-treated Analysis Set (N = 130), disease characteristics were reflective of subjects with R/R FL (Table 13).

The FDA's Assessment:

For the 94 3L+ FL patients included in FDA's primary efficacy analysis, the median age was 63 years (range: 23 to 80 years), 63% were male, Eastern Cooperative Ongology Group performance status was 0 in 64% and 1 in 36% of patients; 55% were White, 9% were Asian and 3% were Black; and 5% were Hispanic and 69% were non-Hispanic. Eighty-nine percent of patients had Stage III to IV disease at study entry, 29% had bulky disease, 32% had refractory disease to the most recent regimen, and 50% had progression of disease within 24 months of initial diagnosis (POD24).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 14: Applicant - Summary of Prior Anticancer Therapies - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Number of lines of prior systemic therapies					
Median	4	2	3	1	2
Q1, Q3	3.0, 4.0	2.0, 2.0	2.0, 4.0	1.0, 1.0	2.0, 4.0
Min, Max	3, 10	2, 2	2, 10	1, 1	1, 10
Number of lines of prior systemic therapies - n (%)					
1	0	0	0	23 (100.0)	23 (17.7)
2	0	48 (100.0)	48 (44.9)	0	48 (36.9)
3	26 (44.1)	0	26 (24.3)	0	26 (20.0)
4	19 (32.2)	0	19 (17.8)	0	19 (14.6)
≥ 5	14 (23.7)	0	14 (13.1)	0	14 (10.8)
Time from start of last systemic regimen prior to liso-cel (years)					
Median	0.97	1.64	1.22	1.84	1.35
Q1, Q3	0.50, 2.34	0.69, 2.21	0.64, 2.24	1.10, 3.15	0.67, 2.59
Min, Max	0.2, 13.1	0.2, 5.6	0.2, 13.1	0.5, 11.3	0.2, 13.1
Prior hematopoietic stem cell transplantation - n (%)					
No	43 (72.9)	31 (64.6)	74 (69.2)	23 (100.0)	97 (74.6)
Yes	16 (27.1)	17 (35.4)	33 (30.8)	0	33 (25.4)

Table 14: Applicant - Summary of Prior Anticancer Therapies - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
If Yes					
Autologous	16 (27.1)	17 (35.4)	33 (30.8)	0	33 (25.4)
Received prior PI3K inhibitors - n (%)					
Yes	26 (44.1)	1 (2.1)	27 (25.2)	0	27 (20.8)
No	33 (55.9)	47 (97.9)	80 (74.8)	23 (100.0)	103 (79.2)
Received prior rituximab and lenalidomide (R2) - n (%)					
Yes	18 (30.5)	5 (10.4)	23 (21.5)	0	23 (17.7)
No	41 (69.5)	43 (89.6)	84 (78.5)	23 (100.0)	107 (82.3)
Last line of prior systemic therapy - n (%)					
PI3K inhibitors	15 (25.4)	1 (2.1)	16 (15.0)	0	16 (12.3)
R2	11 (18.6)	5 (10.4)	16 (15.0)	0	16 (12.3)

Prior therapies include any therapies that were stopped before the Leukapheresis.
Systemic therapy includes chemotherapy, immunotherapy and radioimmunotherapy.
Prior systemic anticancer therapies do not include stem cell transplant but do include conditioning regimens for stem cell transplant.
HSCT is considered a line of systemic therapy but is grouped with preceding chemotherapy regimen and any intervening conditioning regimen including radiation.
Source: ADSL, ADCM, ADCMS

Table 15: Applicant-Summary of Anticancer Therapies for Disease Control - Liso-cel-treated Analysis Set - Study FOL-001

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Anticancer Treatment[a]					
Yes	29 (49.2)	15 (31.3)	44 (41.1)	5 (21.7)	49 (37.7)
No	30 (50.8)	33 (68.8)	63 (58.9)	18 (78.3)	81 (62.3)
Type of Treatment					
Systemic Treatment Only	26 (44.1)	14 (29.2)	40 (37.4)	4 (17.4)	44 (33.8)
Radiotherapy Only	3 (5.1)	1 (2.1)	4 (3.7)	1 (4.3)	5 (3.8)
Systemic Anticancer Medication for Disease Control					
Antineoplastic and Immunomodulating Agents (reported in ≥ 5% of subjects)	26 (44.1)	14 (29.2)	40 (37.4)	4 (17.4)	44 (33.8)
Rituximab	9 (15.3)	9 (18.8)	18 (16.8)	2 (8.7)	20 (15.4)
Cyclophosphamide	10 (16.9)	6 (12.5)	16 (15.0)	1 (4.3)	17 (13.1)
Gemcitabine	7 (11.9)	4 (8.3)	11 (10.3)	1 (4.3)	12 (9.2)
Vincristine	6 (10.2)	5 (10.4)	11 (10.3)	0	11 (8.5)
Oxaliplatin	6 (10.2)	3 (6.3)	9 (8.4)	1 (4.3)	10 (7.7)
Doxorubicin	5 (8.5)	4 (8.3)	9 (8.4)	0	9 (6.9)
Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins (reported in ≥ 2% of subjects)	9 (15.3)	7 (14.6)	16 (15.0)	3 (13.0)	19 (14.6)
Prednisolone	3 (5.1)	2 (4.2)	5 (4.7)	0	5 (3.8)
Prednisone	3 (5.1)	2 (4.2)	5 (4.7)	1 (4.3)	6 (4.6)
Dexamethasone	2 (3.4)	1 (2.1)	3 (2.8)	2 (8.7)	5 (3.8)

[a] Anticancer treatment for disease control is defined as any systemic therapy or radiation therapy provided to subjects for disease control after leukapheresis and before LDC.
Source: ADSL, ADCM, ADCMS

The Applicant's Position:

In the 3L+ group the median number of prior systemic therapies (3; range: 2, 10) was reflective of a heavily pretreated R/R population. In the 2L FL group, the median time from start of frontline chemoimmunotherapy to liso-cel was 1.84 years (Table 14).

The FDA's Assessment:

FDA agrees with Applicant's position.

Bridging Therapies:

Between leukapheresis and administration of liso-cel, 37 out of 94 patients (39%) in primary efficacy population received bridging chemotherapy for disease control. Table 16 below shows the therapies administered as bridging therapies:

Table 16. FDA Analysis of Bridging Therapy Administered for Disease Control in Study FOL-001 (N=94)

Bridging Therapies	n (%)
Rituximab	15(16)
Cyclophosphamide	13(14)
Vincristine	11(12)
Gemcitabine	10(11)
Doxorubicin	9(10)
Oxaliplatin	8(9)
Prednisolone	7(7)
Lenalidomide	4(4)
Obinutuzumab	4(4)
Bendamustine	3(3)
Idelalisib	3(3)
Cisplatin	2(2)
Dexamethasone	2(2)
Methylprednisone	2(2)
Polatuzumab vedotin	2(2)
Betamethasone	1(1)
Duvelisib	1(1)
Etoposide	1(1)
Ibrutinib	1(1)
Umbralisib	1(1)

Source: FDA review of ADCM dataset and JCAR0147-FOL-001 Clinical Study Report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Concomitant Medications In the Liso-cel-treated Analysis Set, 130 (100.0%) subjects received at least one concomitant medication and the most frequently prescribed medications by anatomic therapeutic chemical term were antiinfectives for systemic use (126 [96.9%] subjects; most commonly sulfamethoxazole;trimethoprim in 90 [69.2%] subjects), alimentary tract and metabolism (126 [96.9%] subjects; most commonly ondansetron in 88 (67.7%) subjects), and nervous system (126 [96.9%] subjects; most commonly acetaminophen in 115 [88.5%] subjects) (ADSL, ADCM).

Treatment Compliance: Liso-cel and LDC were administered by trained medical

personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documentation, as well as the subject's medical record and CRF.

The Applicant's Position:

Concomitant medications/procedures received by subjects during the study were consistent with the permitted, prohibited, and required usages specified in the protocol, and were reflective of the underlying medical conditions and AEs that were reported in the study.

The FDA's Assessment:

FDA agrees with Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 17: Applicant - ORR Using FDA Algorithm - Liso-cel-treated Efficacy Analysis Set, Liso-cel-treated Analysis Set, and Leukapheresed (ITT) Set - Study FOL-001

ORR	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
Liso-cel-treated Efficacy Analysis Set	N = 101	N = 23	N = 124
n (%)[a]	97 (96.0)	22 (95.7)	119 (96.0)
95% CI[b]	(90.2, 98.9)	(78.1, 99.9)	(90.8, 98.7)
Liso-cel-treated Analysis Set	N = 107	N = 23	N = 130
n (%)[a]	102 (95.3)	22 (95.7)	124 (95.4)
95% CI[b]	(89.4, 98.5)	(78.1, 99.9)	(90.2, 98.3)
Leukapheresed (ITT) Set	N = 114	N = 25	N = 139
n (%)[a]	105 (92.1)	23 (92.0)	128 (92.1)
95% CI[b]	(85.5, 96.3)	(74.0, 99.0)	(86.3, 96.0)

[a] ORR is defined as the proportion of subjects with an objective response of PR or CR based on the Lugano Classification 2014.

[b] Two-sided 95% confidence interval based on exact Clopper-Pearson method.

Source: ADSL, ADRS

The Applicant's Position:

Overall responses (CR or PR) were high in the 2L+, 3L+, and 2L groups (Table 17). In the 2L+ and 3L+ groups, ORR was consistent across all subgroups, including age, sex, number of prior systemic lines of therapy, POD24 subjects, double refractory subjects, prior R2 treated subjects, and subjects that meet the modified GELF criteria, as expected given the > 90% response rate with almost all subjects responding to treatment (ADSL, ADSUB, ADRS).

The FDA's Assessment:

The Table 18 below summarizes the efficacy data for 94 3L+ subjects, using FDA algorithm and the IRC charter (see Appendix 17.2 and 17.3). The table also summarizes the efficacy result for intention-to-treat (i.e., all leukapheresed population).

Table 18: FDA - Response Rates in Subjects With 3L+ FL Treated With Liso-cel in Study FOL-001

Response Rate	Primary Efficacy Population, per FDA Algorithm* (N=94)	Primary Efficacy Population, per IRC Charter* (N=94)	All Leukapheresed Patients (N=114)
Overall Response Rate*, n (%)	90 (95.7)	91 (96.8)	105 (92.1)
[95% CI]	[89.5, 98.8)	[91.0, 99.3]	[85.5, 96.3]
Complete Response, n (%)	69 (73.4)	88 (93.6)	78 (68.4)
[95% CI]	[63.3, 82.0]	[86.6, 97.6]	[59.1, 76.8)
Partial Response, n (%)	21 (22.3)	3 (3.2)	27(23.7)
[95% CI]	(14.4, 32.1)	[0.7, 9.0]	(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 IRC charter were assessed as per modified Lugano criteria (Appendix 17.2 and 17.3)
**Response per FDA Algorithm represents the IRC assessed response per Lugano (See Appendix 17.2 and 17.3)
Abbreviations: CI: Confidence interval; FL, follicular lymphoma

The efficacy data using FDA algorithm, compared to IRC Charter, includes a change in BOR for a total of 19 subjects (18 from CR to PR and 1 from CR to PD) as shown in Table 19. Efficacy analyses using both methods show similar ORRs. However, the complete response rates (CRRs) are different. Since response assessment using FDA algorithm represents a standard Lugano 2014 classification (Cheson et al. 2014), the clinical review team recommends including response rates as per IRC using FDA algorithm in the label.

Table 19. FDA Analysis of Difference in Best Overall Response (BOR) Using IRC Charter Versus FDA Algorithm

SN	SUBJID	BOR per IRC Charter	BOR per FDA Algorithm	Reason for Discrepancy
1	(b) (6)	CR	PR	No BMB at baseline and at the time of CR
2		CR	PR	No BMB at baseline and at the time of CR
3		CR	PR	No BMB at baseline and at the time of CR
4		CR	PR	No BMB at baseline and at the time of CR
5		CR	PR	No BMB at baseline and at the time of CR
6		CR	PR	BMB at screening with +lymphoma involvement; No repeat BMB at time of CR
7		CR	PR	No BMB at baseline and at the time of CR
8		CR	PR	No BMB at baseline and at the time of CR
9		CR	PR	No BMB at baseline and at the time of CR
10		CR	PR	No BMB at baseline and at the time of CR
11		CR	PR	No BMB at baseline and at the time of CR
12		CR	PR	No BMB at baseline and at the time of CR
13		CR	PR	No BMB at baseline and at the time of CR
14		CR	PR	No BMB at baseline and at the time of CR
15		CR	PD	Evidence of clinical PD
16		CR	PR	No BMB at baseline and at the time of CR
17		CR	PR	No BMB at baseline and at the time of CR
18		CR	PR	No BMB at baseline and at the time of CR
19		CR	PR	No BMB at baseline and at the time of CR

Source: FDA analysis of ADRS dataset, summary of clinical efficacy and JCAR017-FOL001 clinical study report
Abbreviations: BMB Bone marrow biopsy; CR complete response; PR partial response; PD, progressive disease

FDA agrees with Applicant's description of response rates in 2L FL patients which were similar to response rates seen in 3L+ FL patients.

Data Quality and Integrity

The Applicant's Position:

Data review and quality control checks were implemented by the Sponsor and consisted of site monitoring visits guided by the Clinical Management Plan to review source documents against the eCRF and data validation checks of the eCRF and externally loaded data as per the established Data Review Plan. Data quality review was performed to ensure data completeness and data integrity. Any issues or findings were followed up for resolution during Data Quality Subteam meetings and Data Review Meetings. In addition, a review of the database was performed by the Sponsor's GBDS to enhance the quality and ensure completeness of the data. When the database was declared complete and accurate by the CRO and the Sponsor, the CRO's Database Lock Checklist and approval forms were completed, which documented that all prerequisites for the database lock were achieved, and the database was locked.

To facilitate data cleaning in a database lock process, a programmatic cutoff approach was adopted to retain the data given a cutoff date (LSLV). The approach allowed the data cleaning process to focus on ensuring the quality of the data retained to support the analysis. Detailed explanation of the algorithm and pre-specified data cutoff specifications are provided in a separate study-related document.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 20: Applicant – Summary of Secondary Endpoints Efficacy Results Using FDA Algorithm – Liso-cel-treated Efficacy Analysis Set – Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
CRR	N = 53	N = 48	N = 101	N = 23	N = 124
n (%)[a]	39 (73.6)	34 (70.8)	73 (72.3)	16 (69.6)	89 (71.8)
95% CI	(59.7, 84.7)	(55.9, 83.0)	(62.5, 80.7)	(47.1, 86.8)	(63.0, 79.5)
PRR	N = 53	N = 48	N = 101	N = 23	N = 124
n (%)[a]	11 (20.8)	13 (27.1)	24 (23.8)	6 (26.1)	30 (24.2)
95% CI	(10.8, 34.1)	(15.3, 41.8)	(15.9, 33.3)	(10.2, 48.4)	(17.0, 32.7)
DOR, months	N = 50	N = 47	N = 97	N = 22	N = 119
Median (95% CI)[b]	N.A. (18.04, N.A.)	N.A. (N.A., N.A.)	N.A. (18.04, N.A.)	N.A. (19.32, N.A.)	N.A. (19.32, N.A.)
Min, Max[c]	1.9, 23.0+	0.0+, 23.1+	0.0+, 23.1+	4.8, 23.6+	0.0+, 23.6+
Median follow-up (from first response), months (95% CI)[d]	16.89 (16.30, 17.05)	14.29 (12.02, 16.79)	16.59 (15.64, 16.89)	16.79 (14.49, 17.15)	16.66 (16.23, 16.89)
Probability of continued response after initial response (SE) %					
6 months	86.0 (4.907)	87.0 (4.966)	86.5 (3.492)	95.5 (4.441)	88.1 (2.977)
12 months	81.6 (5.542)	81.8 (5.857)	81.7 (4.025)	89.8 (6.866)	83.3 (3.524)
18 months	77.9 (6.413)	78.3 (6.596)	77.9 (4.708)	89.8 (6.866)	80.2 (4.046)
DOR if BOR is CR[e], months	N = 39	N = 34	N = 73	N = 16	N = 89
Median (95% CI)[b]	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
Min, Max[c]	3.0, 23.0+	2.8, 23.1+	2.8, 23.1+	9.2+, 23.6+	2.8, 23.6+
Probability of continued response after initial response (SE) %					
6 months	92.3 (4.267)	91.2 (4.864)	91.8 (3.215)	100.0 (0.000)	93.3 (2.658)
12 months	89.5 (4.971)	87.4 (5.963)	88.6 (3.807)	92.3 (7.391)	89.3 (3.388)
18 months	85.0 (6.429)	82.2 (7.508)	83.6 (5.064)	92.3 (7.391)	85.2 (4.379)
DOR if BOR is PR, months	n = 11	n = 13	n = 24	n = 6	n = 30
Median (95% CI)[b]	18.04 (2.07, N.A.)	N.A. (4.17, N.A.)	18.04 (5.22, N.A.)	19.32 (4.80, N.A.)	18.04 (8.08, N.A.)
Min, Max[c]	1.9, 22.4+	0.0+, 17.6+	0.0+, 22.4+	4.8, 23.1+	0.0+, 23.1+
Probability of continued response after initial response (SE) %					
6 months	63.6 (14.504)	75.0 (12.500)	69.6 (9.594)	83.3 (15.215)	72.4 (8.300)
12 months	53.0 (15.486)	64.3 (14.601)	59.2 (10.608)	83.3 (15.215)	64.3 (9.147)

Table 20: Applicant – Summary of Secondary Endpoints Efficacy Results Using FDA Algorithm – Liso-cel-treated Efficacy Analysis Set – Study FOL-001

	4L+ FL Cohort 1	3L FL Cohort 2	3L+ FL Cohorts 1 + 2	2L FL Cohort 3	Total 2L+ FL Cohorts 1, 2, 3
18 months	53.0 (15.486)	N.A.	59.2 (10.608)	83.3 (15.215)	64.3 (9.147)
PFS	N = 53	N = 48	N = 101	N = 23	N = 124
Events, n (%)	14 (26.4)	10 (20.8)	24 (23.8)	4 (17.4)	28 (22.6)
Median (95% CI), months[b]	N.A. (18.96, N.A.)	N.A.	N.A. (18.96, N.A.)	N.A. (20.21, N.A.)	N.A. (20.21, N.A.)
Min, Max, months[c]	0.8, 24.4+	1.4+, 24.1+	0.8, 24.4+	0.2, 24.5+	0.2, 24.5+
PFS rate, % (SE)[f]					
6 months	83.0 (5.157)	93.6 (3.566)	88.0 (3.245)	91.3 (5.875)	88.6 (2.860)
12 months	77.0 (5.835)	82.7 (5.572)	79.7 (4.064)	91.3 (5.875)	81.9 (3.496)
18 months	73.9 (6.364)	76.6 (6.643)	75.0 (4.667)	85.9 (7.598)	77.2 (4.032)
Median follow-up (from infusion), months (95% CI)[d]	17.81 (17.18, 17.94)	15.21 (12.91, 17.71)	17.58 (16.62, 17.84)	17.77 (15.54, 17.94)	17.58 (17.05, 17.81)

[a] CRR is the proportion of subjects with a BOR of CR. PRR is the proportion of subjects with a BOR of PR.
[b] Median, Q1, Q3 are estimated from KM product-limit estimates
[c] Symbol + indicates a censored value.
[d] Reverse KM method is used to obtain the median follow-up and its 95% confidence intervals.
[e] Per protocol, DOR if BOR is CR is defined as the time from first response (CR or PR) to disease progression or death from any cause up to 60 months after liso-cel infusion (EOS).
[f] Based on KM estimates.
Source: ADSL, ADRS, ADTTE, ADSUB

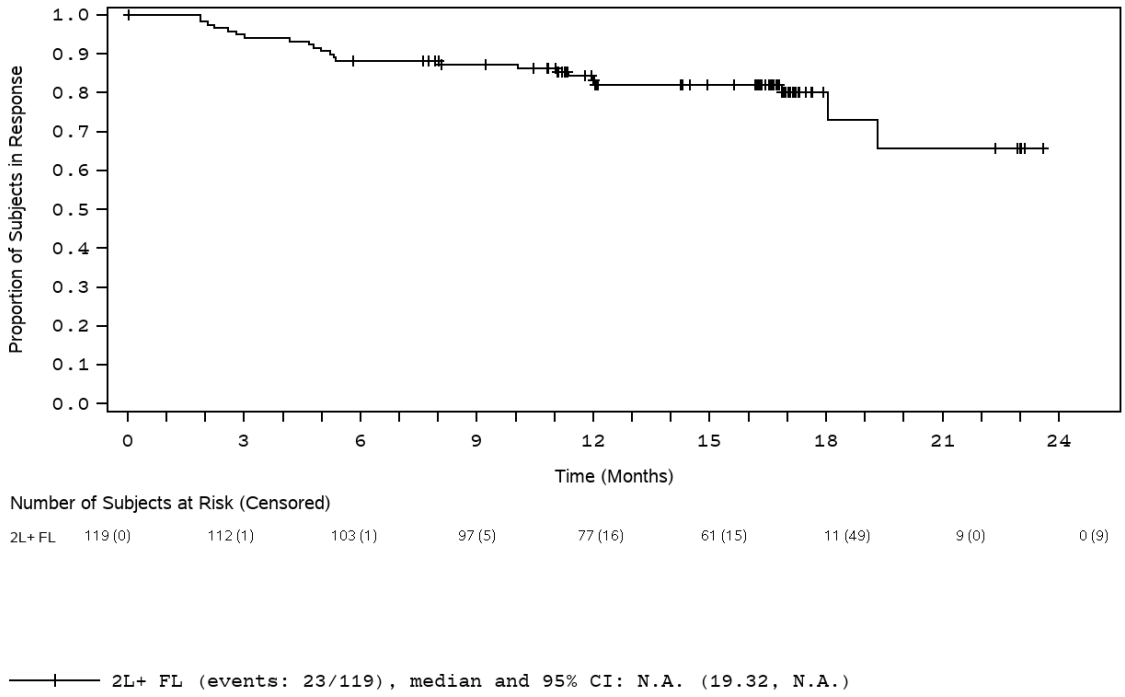
Table 21: Applicant – Overall Survival Summary (Secondary Endpoint) – Liso-cel-treated Efficacy Analysis Set – Study FOL-001

	4L+ FL Cohort 1 N = 53	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 101	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 124
Events, n (%)	7 (13.2)	4 (8.3)	11 (10.9)	1 (4.3)	12 (9.7)
Median (95% CI), months[a]	N.A.	N.A.	N.A.	N.A.	N.A.
Min, Max, months[b]	3.7, 24.4+	5.6, 24.1+	3.7, 24.4+	1.0, 26.3+	1.0, 26.3+
OS rate, % (SE)[c]					
6 months	94.3 (3.174)	97.9 (2.062)	96.0 (1.941)	95.7 (4.252)	96.0 (1.767)
12 months	90.6 (4.015)	93.7 (3.520)	92.1 (2.691)	95.7 (4.252)	92.7 (2.332)
18 months	88.1 (4.625)	93.7 (3.520)	90.6 (3.030)	95.7 (4.252)	91.5 (2.594)

OS is defined as the interval from the date of liso-cel infusion to the date of death due to any reason. The OS analysis includes all available OS information from both the FOL-001 as well as GC-LTFU-001 studies.
[a] Median, Q1, Q3 are estimated from KM product-limit estimates
[b] Symbol + indicates a censored value.
[c] Based on KM estimates.

Source: refer to ADSL, ADTTE

Figure 2: Applicant – KM Plot of DOR Using FDA Algorithm – Liso-cel-treated Efficacy Analysis Set – 2L+ Subjects who Achieved CR or PR – Study FOL-001



Symbols represent censored observations.

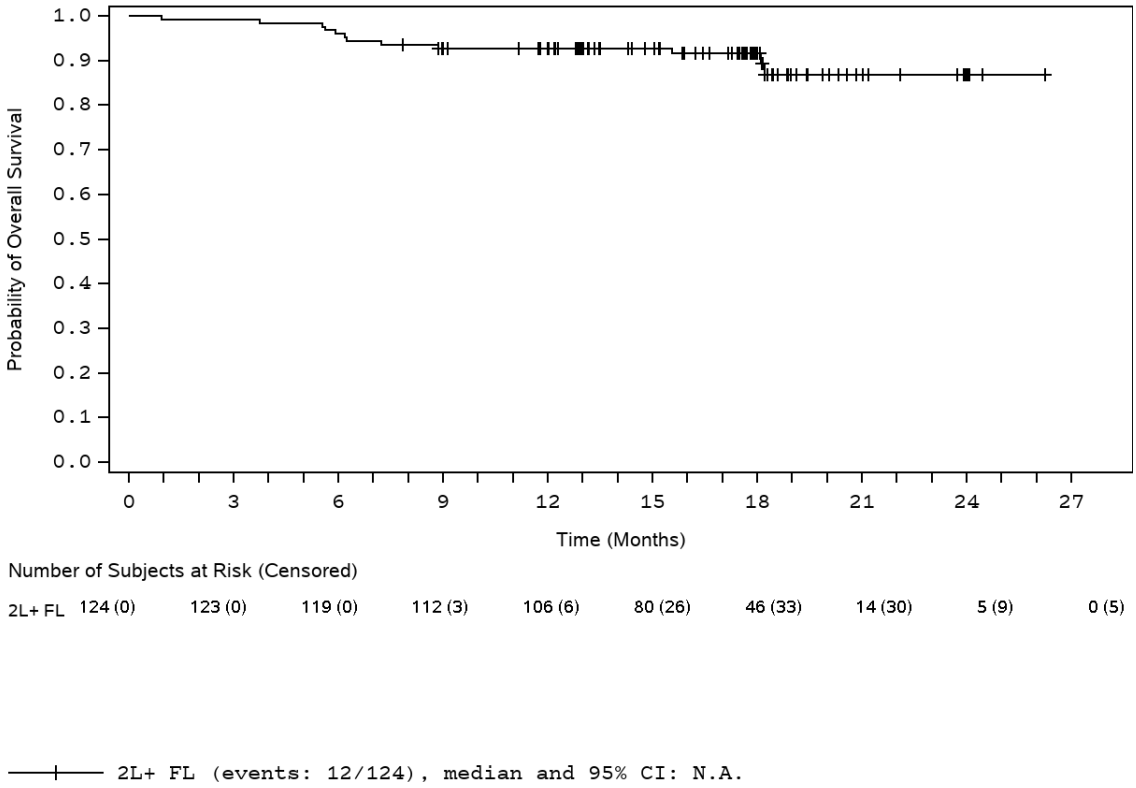
DOR is defined as the interval from the first documentation of response to progressive disease or death from any cause, whichever occurs first.

12 months DOR follow-up measured from the first objective response date to, the last adequate (radiographic) disease assessment (using the 12-month visit window of -30/+90 days), or disease progression or death.

Responders and DOR follow-up status at the time of data cut: Per FDA algorithm (Liso-cel-Treated Efficacy Analysis Set), 3L+ FL subjects: 87 with DOR FU at 12-month visit: 67 ongoing/remain at risk, 17 with disease progression, 3 with death; and 10 with ongoing DOR FU before 12 month visit. 2L FL subjects, 20 with DOR FU at 12-month visit: 17 with ongoing/remain at risk, 3 with disease progression, 0 with death; and 2 with ongoing DOR FU before 12 month visit.

Source: ADSL, ADTTE

Figure 3: Applicant – KM Plot of OS – Liso-cel-treated Efficacy Analysis Set – 2L+ Subjects – Study FOL-001



Symbols represent censored observations.

The OS analysis includes all available OS information from both the FOL-001 as well as the GC-LTFU-001 studies.

Source: ADSL, ADTTE, ADRS

The Applicant's Position:

In the 2L+, 3L+, and 2L groups, the CRR was 71.8%, 72.3%, and 69.6%, respectively (Table 20). In the 2L+ and 3L+ groups, CRR was consistent across all subgroups, including age, sex, number of prior systemic lines of therapy, POD24 subjects, double refractory subjects, prior R2 treated subjects, and subjects that meet the modified GELF criteria, with high CRR in all subgroups (ADSL, ADSUB, ADRS).

Among the 119 responders in the 2L+ group, 107 responders had at least 12 months DOR follow-up measured from the first objective response date to the last adequate (radiographic) disease assessment, or disease progression, or death. In the 3L+ and 2L groups, 87 out of 97 responders and 20 out of 22 responders had at least 12 months DOR follow-up, respectively.

In the 2L+ group, with a median follow-up for DOR of 16.66 months (95% CI: 16.23, 16.89; minimum of 0.0+ to maximum of 23.6+) and a median follow-up for PFS of 17.58 months (95% CI: 17.05, 17.81; minimum of 0.2 to maximum of 24.5+), respectively, the median DOR and PFS were not reached (Table 20 and Figure 2), indicating a clinically meaningful increase in efficacy compared to the historical median

PFS of approximately 12 months or less in this population.[53]

In the 3L+ and 2L groups, subjects the median DOR and PFS were also not reached. The probability of continued response after initial response was observed to be high at 12 months (83.3% 2L+, 81.7% 3L+, and 89.8% 2L) and 18 months (80.2% 2L+, 77.9% 3L+, and 89.8% 2L) in the FL groups. PFS rates were observed to be high at 12 months and 18 months in FL groups (Table 20).

The median OS was not reached in the 2L+, 3L+, and 2L groups and OS rates were observed to be high at 12 months and 18 months (Table 21 and Figure 3).

The efficacy results suggest the potential for deep and durable responses in this high-risk R/R FL population with high unmet need.

The FDA's Assessment:

Table 22 summarizes the DOR data in 3L+ FL patients treated with liso-cel in Study JCAR017-FOL-001.

Table 22: FDA – Duration of Response in 3L+ FL Subjects Treated With Liso-cel in Study FOL-001

DOR Parameter	BREYANZI Treated[a] N=94
Number of Responders	N=90
DOR (months)	-
Median [95% CI][b]	NR (18.04, NR)
Range	1.9, 23.1+
Rate at 12 months, % (95% CI)	80.9 (71.0, 87.7)
Rate at 18 months, % (95% CI)	77.4 (60.6, 87.7)
DOR if best response is CR (months)	N=69
Median [95% CI][b]	NR [NR, NR]
Range	2.8, 23.1+
Rate at 12 months, % (95% CI)	88.2 (77.7, 93.9)
Rate at 18 months, % (95% CI)	83.1 (70.0, 90.9)
DOR if best response is PR (months)	N=21
Median [95% CI][b]	18.04 [4.17, NR]
Range	1.87, 22.4+
Rate at 12 months, % (95% CI)	56.8 (33.3, 74.7)
Rate at 18 months, % (95% CI)	56.8 (33.3, 74.7)
Follow-up for DOR, median (95%CI)	16.8 months (16.3, 17.0)

Source: FDA statistical reviewer's review memo
[a]Evaluable for efficacy.
[b]Median [95% CI] are estimated from KM estimates
+Indicates a censored value.
Abbreviations: DOR, duration of response; CI, confidence interval; CR, complete response; PR, partial response; NR, not reached

Progression Free Survival (PFS) and Overall Survival (OS)

Study JCAR017-FOL-001 is a single-arm study with no comparator group; hence, time-to-event endpoint (such as PFS, OS) data are not interpretable. Therefore, the PFS and OS data have limited value in the benefit-risk assessment and should be interpreted with caution. See statistical reviewer memo for further information on these endpoints.

Dose/Dose Response

The Applicant's Position:
General dosing is discussed in Section 6. Dose response was not evaluated in Study FOL-001.

The FDA's Assessment:

FDA agrees with Applicant's position.

Durability of Response

The Applicant's Position:
Durability of response was demonstrated by the DOR, PFS, and OS (Table 20). Study FOL-001 study is ongoing to follow-up on the long-term efficacy and safety.

The FDA's Assessment:

FDA's analysis of DOR is presented in Table 22.

Persistence of Effect

The Applicant's Position:
With a median follow-up of 18.89 months, Study FOL-001 demonstrated clinical benefit of liso-cel in subjects with R/R FL. Durability of response was demonstrated by the DOR, PFS, and OS.

In the 3L+ group, ORR was high (96.0%) with a high CRR (72.3%) in the Liso-cel-treated Efficacy Analysis Set. With a median follow-up of 16.59 months for DOR and 17.58 months for PFS, the median DOR and PFS were not reached at data cutoff, indicating a clinically meaningful increase in efficacy compared to the historical median PFS of approximately 12 months or less in this population. The median OS was not reached. High PFS and OS rates were observed at 12 and 18 months.

In addition, in the PK Analysis Set, persistence of liso-cel transgene was observed up to Day 730 in the 3L+ group; however, the number of evaluable subjects at Day 730 was small in the 3L+ group (n = 3). Persistence of liso-cel transgene was 44.9% (22 of 49) at Day 545 in the 3L+ group.

B-cell aplasia (ie, CD19+ B-cells < 3% of peripheral blood lymphocytes) was observed in 75.7% of subjects at baseline in the 3L+ group and increased to 99.0% of subjects by Day 8, was maintained in over 90% of subjects through Day 90.

The FOL-001 study is ongoing to follow-up on the long-term efficacy and safety of liso-cel in R/R FL.

The FDA's Assessment:

Results from Study FOL-001 demonstrated durable response in 3L+ FL patients treated with liso-cel after a median follow up of 16.8 months.

Responses (CR or PR) per IRC were achieved in 90 out of 94 subjects, with the estimated probability of remaining in response at 12 months being 80.9% (95% CI:

71.0, 87.7). Sixty-nine subjects achieved a BOR of CR, and the estimated probability of remaining in CR at 12 months was 88.2% (95% CI: 77.7, 93.9)

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

EORTC QLQ-C30 – Mean Change from Baseline

In all predefined primary domains of interest, after an initial deterioration, liso-cel consistently demonstrated improvements over time in evaluations of group-level mean change from baseline on EORTC QLQ-C30 domains in the 4L+, 3L+, and 2L groups (ADSL, ADQS). The mean changes exceeded the threshold for clinically meaningful improvement at some visits. These findings were similar between the remaining EORTC domains. In individual level analyses, from Day 29 onwards, most subjects (~65% to 100%) experienced clinically meaningful improvement or no change across all subgroups on the primary domains of EORTC QLQ-C30 (ADSL, ADQS).

FACT-LymS – Mean Changes from Baseline

Subjects treated with liso-cel showed improvement in lymphoma specific symptoms as assessed by FACT-LymS as early as Day 29 and remaining largely consistent thereafter in the 3L+ group, with similar trends in the 4L+ and 2L groups. The mean changes exceeded the threshold for clinically meaningful improvement at some visits. In individual level analyses, from Day 29 onward, most subjects (~60% to 100%) experienced clinically meaningful improvement or no change across all subgroups on the FACT-LymS (ADSL, ADQS).

EQ-5D-5L Summary Index

Subjects showed improvement in the EQ-5D-5L summary index between Day 1 to Day 29 and remaining consistent thereafter in 3L+ subjects, with a similar trend in 4L+ subjects. In 2L subjects there was a trend towards improvement at Day 15, 60, and 365, whereas other timepoints were stable compared to baseline. The improvements did not reach the clinically meaningful improvement threshold (ADSL, ADQS).

Hospital Resource Utilization

Hospitalization may have been required after treatment with liso-cel to manage any treatment-associated toxicities. Administration of liso-cel as inpatient or outpatient setting was determined at the Investigator's discretion (ADSL, ADEX, ADEXS, ADHO).

In the 115 (82.7%) subjects who received liso-cel and who were monitored as inpatients, the most common reason for hospitalization during liso-cel infusion was other (prophylaxis for CAR T cell administration) (95 [82.6%] subjects). For these 115 subjects, the median duration of hospitalization from liso-cel administration was 15 days (range, 4 to 41). No subjects were admitted to the ICU during liso-cel administration (ADSL, ADHO, ADHOS).

In the 15 (10.8%) subjects who received liso-cel and were monitored as outpatients, 7 (46.7%) subjects were hospitalized after liso-cel administration; 7 (100%) were hospitalized due to an AE. The median time from liso-cel administration to first

hospitalization was 7 days (range, 4 to 16). None of these subjects had ICU stays (ADSL, ADHO, ADHOS).

The FDA's Assessment:

The Applicant submitted patient-reported outcomes data collected using three different instruments (Functionality Assessment of Cancer Therapy Lymphoma Subscale questionnaire, European Organization for Research and Treatment of Cancer – Quality of Life C30 questionnaire and European Quality of Life 5 Dimensions health state classifier to 5 levels Utility Index). However, because the study is a single-arm study with no comparator arm, the patient-reported outcome data is descriptive and is not considered for regulatory decision making. The data will not be included in the USPI.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not applicable.

8.1.3 Integrated Review of Effectiveness

The FDA's Assessment:

The efficacy result from Study JCAR017-FOL-001 formed the sole basis for efficacy claim of liso-cel in treatment of R/R FL. No additional efficacy data from other studies were submitted for review. Therefore, no integrated review of effectiveness or pooling of efficacy data were performed.

8.1.4 Assessment of Efficacy Across Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not performed. See FDA position Section 8.1.3.

8.2 Review of Safety

8.2.1 Safety Review Approach

The Applicant's Position:
Safety data are provided for 130 subjects with R/R FL treated with liso-cel monotherapy enrolled in Cohorts 1, 2, and 3 (referred to as 2L+ FL) in Study FOL-001 and are the focus of Section 8.2.2 to 8.2.7.

To demonstrate consistency in safety across indications, the safety profile of liso-cel in

the FL population (pooled Cohorts 1, 2, and 3) are also presented side-by-side to the pooled safety population of 3L+ LBCL plus 2L LBCL (Table 35).

The FDA's Assessment:

During the safety review, adverse drug reactions are defined as any treatment-emergent adverse event (TEAE) with onset or worsening after the start of liso-cel infusion, regardless of perceived relationship and causality with liso-cel.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1, and AE severity was graded using the National Cancer Institute's Common Terminology for Adverse Events version 5.0. CRS severity was graded according to the grading scale adapted from Lee (Lee et al. 2014). The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs.

To minimize such underestimation of AEs, FDA grouped preferred terms that represent the same disease process (please see Appendix 17.1 for the list of FDA Grouped Terms). The review team utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar products within this class of therapies. Analyses were performed using JMP 17.0.0 (SAS Institute, Inc.).

In general, all grade AEs were counted by maximum toxicity (max tox) grade (i.e., multiple incidences of the same AE in one subject are counted once at the worst grade for this subject). For example, for Grade 3 AEs, the number of subjects who experienced any event with max tox Grade of 3 is counted. This is different from the number of subjects who had a Grade 3 event, which is typically larger, as some also had Grade 4 or 5 events.

FDA's safety review focused on:

1) Primary Safety Population from Study FOL-001: includes 107 FL patients with 2 or more prior lines of systemic therapies (Cohort 1 and 2), treated with conforming liso-cel.
2) R/R high risk FL patients with 1 prior line of therapy (high risk 2L FL in Cohort 3 of FOL-001 study)
3) Integrated Safety Population: includes 956 liso-cel treated patients:
    - 577 LBCL patients included in the current USPI (3L+ LBCL [017001 DLBCL Cohort, 017007 DLBCL and BCM-001] plus 2L LBCL [BCM-003 and 017006]).
    - 118 R/R CLL/SLL patients.
    - 107 FL patients after 2 or more prior lines of therapy.
    - 23 high risk FL patients after 1 prior line of therapy.

The integrated safety dataset is considered supportive only.

The clinical review of the safety for this BLA is based on the following:

- ADAM datasets
- Case report forms and safety narratives

The primary safety analysis for labeling purposes was conducted on safety analysis set from Study JCAR017-FOL-001 which comprised 107 FL patients with 2 or more prior lines of systemic therapy who were treated with a single dose of conforming liso-cel with a data cutoff date of January 23, 2023.

Table 25 summarizes the demographics and baseline characteristics of the safety population. Overall, among all subjects, the median age was 62 years (range: 23 to 80 years), 38% were female, and Eastern Cooperative Ongology Group performance status was 0 in 61% and 1 in 39% of patients; 56% were White, 3% were Black, 9% were Asian; 5% were Hispanic and 69% were non-Hispanic.

Furthermore, the review process also involved the review of 90-day safety report submitted by the Applicant on February 13, 2024, with the data cutoff date of April 27, 2023.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 23: Applicant – Exposure to LDC – Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Fludarabine					
Subjects who Received Full Dose of Fludarabine[a] – n (%)	52 (88.1)	43 (89.6)	95 (88.8)	22 (95.7)	117 (90.0)
Adjusted Dose of Fludarabine[b] – n (%)	7 (11.9)	5 (10.4)	12 (11.2)	1 (4.3)	13 (10.0)
Cyclophosphamide					
Subjects who Received Full Dose of Cyclophosphamide[a]- n (%)	58 (98.3)	48 (100.0)	106 (99.1)	23 (100.0)	129 (99.2)
Adjusted Dose of Cyclophosphamide[b] – n (%)	1 (1.7)	0	1 (0.9)	0	1 (0.8)
Time From Last Dose of Lymphodepleting Chemotherapy to Liso-cel Infusion (Days)					
n	59	48	107	23	130
Median	4	4	4	4	4

Table 23: Applicant – Exposure to LDC – Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Q1, Q3	4.0, 5.0	4.0, 4.0	4.0, 5.0	4.0, 4.0	4.0, 5.0
Min, Max	3, 12	4, 7	3, 12	3, 7	3, 12

[a] Received full dose, no missing doses.
[b] Received at least one adjusted dose but did not miss a dose.
Source: ADSL, ADEX, ADEXS

Table 24: Applicant – Liso-cel Exposure – Liso-cel-treated Analysis Set

	4L+ FL Cohort 1 N = 59	3L FL Cohort 2 N = 48	3L+ FL Cohorts 1 + 2 N = 107	2L FL Cohort 3 N = 23	Total 2L+ FL Cohorts 1, 2, 3 N = 130
Liso-cel CD8+ Cells					
Total Number of Liso-cel CD8+ Cell Counts Infused (10^6 Cells)					
Median	49.9	49.76	49.82	50.11	49.85
Min, Max	42.3, 51.7	47.9, 51.6	42.3, 51.7	48.1, 51.7	42.3, 51.7
Liso-cel CD4+ Cells					
Total Number of Liso-cel CD4+ Cell Counts Infused (10^6 Cells)					
Median	50.2	49.75	49.99	50.29	50.02
Min, Max	43.1, 58.8	48.0, 52.0	43.1, 58.8	47.9, 52.0	43.1, 58.8
Combined Liso-cel Dose					
Total Number of Liso-cel CD4+ And CD8+ Cell Counts Infused (10^6 Cells)					
Median	100.13	99.73	100.02	99.92	100.02
Min, Max	93.4, 109.2	96.6, 101.8	93.4, 109.2	97.4, 102.9	93.4, 109.2

Source: ADSL, ADEX, ADEXS, ADHO, SDTM.FA, SDTM.SUPPFA

The Applicant's Position:

LDC: The median time from end of LDC to liso-cel infusion (4 days; range, 3 to 12) was consistent with the protocol-specified time (2 to 7 days) (Table 23).

Manufacturing: In the Leukapheresed Set, the median time from leukapheresis to liso-cel availability (defined as the date of release for infusion and represents the date the product was available to ship) was 29 days (range: 19 to 55). The median time from leukapheresis to liso-cel infusion day was 49 days (range: 31 to 313). Manufacturing failure rate (defined as number of subjects for whom liso-cel product [conforming at time of release] could not be manufactured / number of subjects who had leukapheresis and manufacturing information available x 100; rejected lots are

excluded from the calculation) was infrequent (4.3% of subjects).

Liso-cel treatment: The median number of total liso-cel administered dose cell counts across all cohorts (100.02 × 10^6 CAR+ T cells [range: 93.4 × 10^6 to 109.2 × 10^6]) was consistent with the protocol-specified dose of 100 × 10^6 CAR+ T cells (Table 24).

The FDA's Assessment:

FDA agrees with Applicant's assessment. Liso-cel doses administered were within the proposed marketing dose rate of 90 to 110 × 10^6 CAR+ viable T cells. In 107 3L+ FL patients included in FDA's safety analysis, the median dose administered was 100.02 × 10^6 CAR+ T cells [range: 93.4 × 10^6 to 109.2 × 10^6].

Relevant Characteristics of the Safety Population:

The Applicant's Position:
The demographics and baseline characteristics of the Liso-cel-treated Analysis Set (N = 130) were reflective of subjects with R/R FL. Details are provided in Section 8.1.2.

The FDA's Assessment:

The clinical safety review was based primarily on analysis of data including 107 subjects from Cohort 1 and Cohort 2 (3L+ FL) treated with a single, conforming dose of liso-cel after receiving lymphodepleting chemotherapy (LDC); the study data cutoff date was January 23, 2023. Baseline demographics are shown in Table 25.

Table 25. FDA Analysis of Demographic Characteristics of Safety Population From Study FOL-001

Parameters	3L+ FL (N=107)	2L FL (N=23)
Age in years, median (range)	62 (23-80)	53 (34-69)
Female, n (%)	41 (38)	6 (26)
Race, n (%)	-	-
White	60 (56)	9 (39)
Black or African American	3 (3)	1 (4)
Asian	10 (9)	2 (9)
Other/not reported	34 (32)	11 (48)
Ethnicity, n (%)	-	-
Non-Hispanic/Latino	74 (69)	15 (65)
Hispanic/Latino	5 (5)	1 (4)
Not reported	28 (26)	7 (30)
ECOG, n (%)	-	-
0	65 (61)	17 (74)
1	42 (39)	6 (26)

Source: FDA analysis of ADSL data from study FOL-001
Abbreviations; FL, follicular lymphoma

Adequacy of the safety database:

The Applicant's Position:

The number of patients in the Liso-cel-treated Analysis Set is adequate to provide an estimate of adverse reactions that may be associated with liso-cel use in the R/R FL population.

The population studied in Study FOL-001 is representative of an R/R FL population; this is supported by the study population demographic and baseline characteristics. With a sample size of 130 subjects and a median study follow-up of 18.89 months, the exposure of study treatments are sufficient to characterize the safety profile of liso-cel. The routine clinical and laboratory evaluations performed in the study were appropriate to evaluate and characterize the safety profile of liso-cel.

The FDA's Assessment:

The safety from 107 3L+ FL patients provided reasonable data to inform safety of liso-cel for the intended population. Additionally, supportive integrated safety analysis from 23 2L FL along with safety data from patients with LBCL and CLL/SLL indicated a favorable profile of liso-cel.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review. The submission included narratives for AESIs as agreed with FDA. A safety update report will be provided as additional follow-up in the timeframe to be agreed with FDA.

The FDA's Assessment:

FDA agrees with Applicant. The Applicant submitted a 90-day safety update in a timely manner.

Categorization of Adverse Event

The Applicant's Position:
All Aes were coded using MedDRA Version 25.1. The severity of each AE was graded by the Investigator using NCI CTCAE Version 5.0. If NCI CTCAE criteria did not exist for a given event, the Investigator used one of the following: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum severity of the AE. CRS toxicity was graded according to the Lee criteria[54], and individual CRS signs and symptoms were graded according to NCI CTCAE Version 5.0. NT were not graded by the site on the eCRF AE page, but the individual NT signs and symptoms were graded according to the NCI CTCAE. TLS was graded according to Cairo-Bishop.[55]

Aes were analyzed with a focus on TEAEs, defined as any AE that began from the date of liso-cel infusion through and including 90 days after. Any AE that occurred after the initiation of another anticancer treatment was not considered a TEAE. Aes that occurred from screening to prior to liso-cel infusion, and Aes during the post-treatment emergent

period were also analyzed.

AE relatedness to liso-cel or LDC regimen was reported as per the Investigator's assessment. The incidences of TEAEs were summarized by MedDRA SOC and PT for any TEAE, most frequent TEAEs (≥ 5% by PT), any Grade ≥ 3 TEAE, any treatment-related TEAE, any treatment-related Grade ≥ 3 TEAE, any SAE, any treatment-related SAE, any AE leading to death, and treatment-related TEAE leading to death.

AESI are Aes that are known to be associated with the therapeutic class of CAR T-cell therapies that required close monitoring and rapid communication by the investigator to the Sponsor. AESIs for liso-cel included: CRS, iiNT, MAS, TLS, infusion-related reactions, Grade ≥ 3 infections, hypogammaglobulinemia, autoimmune disorders, SPM, and prolonged cytopenias. Time to onset and resolution of the first CRS or iiNT were summarized. Multiple events in an AESI category occurring close to each other were considered as a single episode. Subjects with any unresolved event in the episode were excluded from the analysis of time to resolution of an AESI.

The number of subjects who received tocilizumab or corticosteroids or other anti-cytokine therapy for CRS or iiNT treatment was summarized. Time from onset of CRS or iiNT to the start of tocilizumab or corticosteroids treatment were summarized using descriptive summary statistics.

Pooled Analyses:
The integration of safety data from subjects treated with liso-cel monotherapy is justified due to the following similarities in study design and dose regimen:

- Common-dose regimens for LDC and liso-cel
- Similar safety endpoints
- Similar safety assessment timepoints
- AESI, toxicity gradings, and TEAE definitions and toxicity gradings are consistent across studies

The FDA's Assessment:

FDA agrees with the Applicant's position.

Routine Clinical Tests

The Applicant's Position:
Clinical laboratory evaluations included hematology, coagulation, chemistries, viral serology (anti-SARS-CoV-2), serum pregnancy, inflammatory markers, immunoglobulins, PVS monitoring, and RCL testing.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.4 Safety Results

Table 26: Applicant – Overall Summary of Safety in Study FOL-001

	Number (%) Subjects				
Safety Parameter	**4L+ FL Cohort 1**	**3L FL Cohort 2**	**3L+ FL Cohorts 1 + 2**	**2L FL Cohort 3**	**Total 2L+ FL Cohorts 1, 2, 3**
Leukapheresed Set	**N = 65**	**N = 49**	**N = 114**	**N = 25**	**N = 139**
Deaths	8 (12.3)	5 (10.2)	13 (11.4)	1 (4.0)	14 (10.1)
Primary Cause of Death					
PD	3 (4.6)	2 (4.1)	5 (4.4)	0	5 (3.6)
AE[a]	3 (4.6)	0	3 (2.6)	1 (4.0)	4 (2.9)
Cardiac Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Other[b]	0	3 (6.1)	3 (2.6)	0	3 (2.2)
New Malignancy, or Complications from New Malignancy	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Liso-cel-treated Analysis Set	**N = 59**	**N = 48**	**N = 107**	**N = 23**	**N = 130**
Subjects with any TEAE[c]	58 (98.3)	47 (97.9)	105 (98.1)	23 (100.0)	128 (98.5)
Grade ≥ 3	47 (79.7)	36 (75.0)	83 (77.6)	14 (60.9)	97 (74.6)
Grade 5	0	0	0	1 (4.3)	1 (0.8)
Serious	15 (25.4)	13 (27.1)	28 (26.2)	4 (17.4)	32 (24.6)
Liso-cel-related	54 (91.5)	41 (85.4)	95 (88.8)	19 (82.6)	114 (87.7)
Liso-cel-related serious TEAE	13 (22.0)	9 (18.8)	22 (20.6)	3 (13.0)	25 (19.2)
Liso-cel-related Grade ≥ 3	33 (55.9)	31 (64.6)	64 (59.8)	13 (56.5)	77 (59.2)
Liso-cel-related Grade 5	0	0	0	1 (4.3)	1 (0.8)
LDC-related	48 (81.4)	30 (62.5)	78 (72.9)	17 (73.9)	95 (73.1)
Subjects with any AESI	39 (66.1)	32 (66.7)	71 (66.4)	14 (60.9)	85 (65.4)
CRS	35 (59.3)	28 (58.3)	63 (58.9)	12 (52.2)	75 (57.7)
Median Time to First Onset of CRS[d], days (range)	5 (1, 17)	6 (1, 12)	6 (1, 17)	6 (2, 9)	6 (1, 17)
Median Time to Resolution of First CRS[e], days (range)	3 (1, 9)	4 (1, 10)	4 (1, 10)	3 (2, 7)	3 (1, 10)
Maximum Toxicity Grade					
Grade 1	28 (47.5)	20 (41.7)	48 (44.9)	7 (30.4)	55 (42.3)
Grade 2	6 (10.2)	8 (16.7)	14 (13.1)	5 (21.7)	19 (14.6)
Grade 3	1 (1.7)	0	1 (0.9)	0	1 (0.8)
iiNT[f]	8 (13.6)	8 (16.7)	16 (15.0)	4 (17.4)	20 (15.4)
Median Time to First Onset of iiNT[g], days (range)	9 (4, 13)	8 (7, 16)	8.5 (4, 16)	8.5 (6, 11)	8.5 (4, 16)
Median Time to Resolution of First iiNT[h], days (range)	5 (1, 17)	3 (2, 8)	4.5 (1, 17)	2.5 (1, 4)	3.5 (1, 17)
Maximum Toxicity Grade					
Grade 1	5 (8.5)	7 (14.6)	12 (11.2)	3 (13.0)	15 (11.5)
Grade 2	2 (3.4)	0	2 (1.9)	0	2 (1.5)
Grade 3	1 (1.7)	1 (2.1)	2 (1.9)	1 (4.3)	3 (2.3)

Table 26: Applicant – Overall Summary of Safety in Study FOL-001

	Number (%) Subjects				
Safety Parameter	**4L+ FL Cohort 1**	**3L FL Cohort 2**	**3L+ FL Cohorts 1 + 2**	**2L FL Cohort 3**	**Total 2L+ FL Cohorts 1, 2, 3**
IRR	0	0	0	0	0
MAS	0	0	0	1 (4.3)	1 (0.8)
TLS	0	0	0	0	0
Hypogammaglobulinemia	2 (3.4)	3 (6.3)	5 (4.7)	1 (4.3)	6 (4.6)
Grade ≥ 3 infections	3 (5.1)	4 (8.3)	7 (6.5)	0	7 (5.4)
SPM	2 (3.4)	1 (2.1)	3 (2.8)	1 (4.3)	4 (3.1)
Autoimmune disorders	0	0	0	0	0
Prolonged cytopenia[i]	14 (23.7)	12 (25.0)	26 (24.3)	3 (13.0)	29 (22.3)

[a] Death from AE (NOS) included: Cohort 1: acute respiratory failure hypoxic (LDC-infusion), acute myeloid leukemia (from Day 91 after infusion), progressive multifocal leukoencephalopathy (from Day 91 after infusion), and Cohort 3: HLH (Day 1-30).

[b] Death from other cause included: Cohort 2: 2 cases of COVID-19 and erythema multiform.

[c] A TEAE was defined as an AE that started any time from initiation of liso-cel administration through and including 90 days following liso-cel administration.

[d] Time to onset is calculated from liso-cel infusion to the first onset of a CRS event.

[e] Any CRS events that stop/start within 7 days (start date-stop date ≤ 7) will be considered in a single episode. Time to resolution of CRS is defined when the last CRS event of the first episode end. Subjects with an unresolved event in the episode are excluded from descriptive statistics summary.

[f] iiNT was captured using the preferred term Neurotoxicity and graded using NCI CTCAE v.5.0 on the basis of the highest individual symptom grade.

[g] Time from the latest liso-cel infusion to the 1st onset of an iiNT event.

[h] Any iiNT events with (start date-stop date ≤ 7) are considered in a single episode. Time to resolution is defined when the last iiNT event of the 1st episode ends. Subjects with an unresolved event in the episode are excluded.

[I] Defined as Grade ≥ 3 cytopenia at the Day 29 (± 2 days) visit based on central laboratory assessments of neutropenia, thrombocytopenia, or anemia.

Source: ADSL, ADAE, ADCPT, ADAETTE, ADAES

Deaths

Data:

Table 27: Applicant -Summary of Deaths and Causes – Leukapheresed Analysis Set

Primary Cause	4L+ FL Cohort 1 N = 65 n (%)	3L FL Cohort 2 N = 49 n (%)	3L+ FL Cohorts 1 + 2 N = 114 n (%)	2L FL Cohort 3 N = 25 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 139 n (%)
Overall Number of Deaths	8 (12.3)	5 (10.2)	13 (11.4)	1 (4.0)	14 (10.1)
Cause of Death					
PD	3 (4.6)	2 (4.1)	5 (4.4)	0	5 (3.6)
Death From AE (Not Otherwise Specified)[a]	3 (4.6)	0	3 (2.6)	1 (4.0)	4 (2.9)
Death From Cardiac Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Death From Other Cause[b]	0	3 (6.1)	3 (2.6)	0	3 (2.2)
Death From New Malignancy, Or Complication From New Malignancy	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Death					
Between Leukapheresis and LDC Start[c]	0	0	0	0	0
Between LDC And Infusion[d]	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Death From Adverse Event (Not Otherwise Specified)	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Infusion, Day 1- 30[e]	0	0	0	1 (4.0)	1 (0.7)
Death From Adverse Event (Not Otherwise Specified)	0	0	0	1 (4.0)	1 (0.7)
Infusion, Day 31- 90[f]	0	0	0	0	0
From Infusion, Day 91[g]	7 (10.8)	5 (10.2)	12 (10.5)	0	12 (8.6)
Death From Malignant Disease Under Study, Or Complication Due To Malignant Disease Under Study	3 (4.6)	2 (4.1)	5 (4.4)	0	5 (3.6)
Death From Adverse Event (Not Otherwise Specified)	2 (3.1)	0	2 (1.8)	0	2 (1.4)
Death From Cardiac Event	1 (1.5)	0	1 (0.9)	0	1 (0.7)
Death From Other Cause	0	3 (6.1)	3 (2.6)	0	3 (2.2)
Death From New Malignancy, Or Complication	1 (1.5)	0	1 (0.9)	0	1 (0.7)

[a] Death from AE (NOS) included: Cohort 1: acute respiratory failure hypoxic (LDC-infusion), acute myeloid leukemia (from Day 91 after infusion), progressive multifocal leukoencephalopathy (from Day 91 after infusion), and Cohort 3: HLH (Day 1-30).
[b] Death from other cause included: Cohort 2: 2 cases of COVID-19 and erythema multiform.
[c] If LDC start date is not available, death is included in this section.
[d] If LDC start date is available and infusion date is not available, death is included in this section.
[e] This period is defined from the first day of infusion until Day 30 after infusion.
[f] This period is defined from Day 31 until Day 90 after infusion.
[g] This period is defined from Day 91 after infusion.
Deaths in long-term follow-up study are included.

Source: ADSL

The Applicant's Position:

In the Leukapheresed Set, 14 (10.1%) subjects died during study: 1 (0.7%) subject from Cohort 1 died between LDC and before liso-cel infusion (due to occurrence of acute respiratory failure, assessed as not related to liso-cel/LDC/study procedure), 1 (0.7%) subject from Cohort 3 died after liso-cel infusion, within 30 days after liso-cel infusion (due to occurrence of HLH assessed as related to liso-cel treatment by the investigator), and 12 (8.6%) subjects died after the 90-day post-infusion period (from Day 91 after infusion) (mainly due to disease progression). One subject from Cohort 1 died due to PML on Day 190 and this event was considered as related to fludarabine and liso-cel by the investigator (Table 27).

One (0.8%) subject experienced a TEAE that led to death: HLH in the 2L FL cohort assessed as related to liso-cel treatment by the investigator. The fatal event was preceded by cytomegalovirus reactivation (diagnosed on Day 18) which could have contributed to HLH (ADSL, ADAE).

The FDA's Assessment:

During the course of FOL-001, there were a total of 14 deaths reported at the time of the study data cutoff date, January 23, 2023. Five of these deaths were related to disease progression. One patient died after receiving LDC, and another patient (2L) died on Day 29 from hemophagocytic lymphohistiocytosis (HLH).

Brief narratives of deaths, not due to disease progression, are described below:

1) Subject (b) (6) Death due to Acute Respiratory Failure, 9 days after initiating lymphodepleting chemotherapy with fludarabine and cyclophosphamide:
   - 69-year-old female (fourth-line or later treatment [4L+]) developed shortness of breath 2 days after receiving LDC, and prior to receiving liso-cel.
   - Admitted to intensive care with Grade 4 Acute Respiratory Failure.
   - Testing positive for enterovirus-rhinovirus infection.
   - Subject diagnosed with drug-induced non-specific interstitial pneumonia.
   - Subject did not have history of cardiac disease or previous oxygen requirement.
   - Code status changed to do not resuscitate.
   - Subject died 9 days after initiating LDC.
2) Subject (b) (6) Death due to Erythema Multiforme Day 489
   - 65-year-old male (3L) who received non-conforming dose of lisocabtagene.
   - Day 22 developed Grade 2 rhabdomyolysis, which required prolonged hospitalization; resolved on Day 86.
   - Subject additionally with prolonged cytopenias, including Grade 4 neutropenia and Grade 4 thrombocytopenia.
   - Day 489 subject died from erythema multiforme; an autopsy was not performed.
   - Per investigator, erythema multiforme confirmed on biopsy results and skin

imaging data; felt to be secondary to a drug eruption, but not related to liso-cel.
- BOR CR on Day 170 (PR Day 24, but no BM done at that time). Subject was still in CR as of last assessment on Day 373.

3) Subject (b) (6) Death due to coronavirus disease 2019 (COVID-19) on Day 169

- 70-year-old male (3L) received liso-cel without complications.
- Subject was in CR at Day 28 and remained in CR at last evaluation (Day 89).
- Subject died from COVID-19 on Day 169.

4) Subject (b) (6) Death due to COVID-19 Pneumonia on Day 551

- 70-year-old male (3L) received liso-cel without complications.
- Day 29 evaluation PR due to lack of BM; marrow Day 58 negative.
- Day 100 subject with CR.
- Day 184 subject with progressive disease (PD).
- Subject died Day 551 from COVID-19 pneumonia.

5) Subject (b) (6) Death due to heart failure on Day 171

- 53-year-old female (4L+) received liso-cel without complications.
- Experienced hypotension during lymphodepletion and again on Day 2, which resolved with sodium chloride.
- Day 29 evaluation with stable disease; subject deemed a non-responder.
- Subject had no further evaluations.
- Died Day 171 due to heart failure.
- History of Grade 1 cardiomyopathy diagnosed approximately 1 year prior to liso-cel infusion.

6) Subject (b) (6) Death due to HLH on Day 29

- 66-year-old male (2L) received liso-cel infusion Day 1 with no complications.
- Day 2 diagnosed with Grade 1 CRS with fever; started tocilizumab.
- Day 5 CRS worsened to Grade 2 with chills, hypotension, tachycardia, and shortness of breath; labs revealed elevated ferritin.
- Day 6 underwent CT imaging, which revealed bilateral pleural effusion and body wall edema.
- Day 7 diagnosed with Grade 4 HLH (related to liso-cel); underwent thoracentesis same day which revealed malignant pleural fluid consistent with subject's known B-cell lymphoma. CRS resolved.
- Day 10 developed Grade 4 allergy to immunoglobulin therapy and was intubated for impending respiratory collapse.
- Day 11 subject was extubated.
- Day 17 elevated quantitative cytomegalovirus deoxyribonucleic acid.
- Day 18 initiated letermovir for cytomegalovirus reactivation
- Day 20 BM biopsy with hypocellular marrow and hypoplasia.
- Day 26 subject experienced bacteremia and veno-occlusive liver disease.
- Day 27 subject experienced disseminated intravascular coagulation, multiple

organ dysfunction.
- Day 29 subject died from HLH.
- BOR: PD.

7) Subject (b) (6) Death due to Grade 5 Progressive Multifocal Leukoencephalopathy (PML) Day 190

- 44-year-old female (4L+) received LDC and liso-cel infusion on Day 1 with no complications.
- ~ Day 90, subject presented with a 2-week history of tremor, fatigue and peripheral neuromuscular weakness.
- Day 122: magnetic resonance imaging of the head demonstrated abnormalities consistent with PML.
- Day 127 developed left-sided weakness and reduced coordination; underwent lumbar puncture which demonstrated cerebral spinal fluid positive for John Cunningham virus by PCR. Subject diagnosed with Grade 4 PML.
- Day 190 subject died of PML.
- BOR: CR
- Subject had been diagnosed with posterior reversible encephalopathy syndrome (PRES) ~ 1 year prior to treatment with liso-cel; she had no residual neurologic sequale prior to LDC/liso-cel with a normal neurologic examination.

8) Subject (b) (6) Death due to Acute Myeloid Leukemia (AML)

- 57-year-old female (4L+) received liso-cel without complications.
- Day 29 evaluation of PR.
- Day 97 evaluation with PD.
- Day 308 subject started treatment for progressive FL with polatuzumab vedotin.
- Day 359 subject underwent BM evaluation which demonstrated AML. "*The hypercellular marrow (80%) was reported to be consistent with treatment-related AML (45% blasts). Cytogenetics showed complex monosomy karyotype with 5q- and -5 on fish."* Tumor tissue was not available for transgene analysis.
- Day 378: replication-competent lentivirus (RCL) testing on blood was negative.
- Day 474 subject died from AML; no treatment was given.

9) Subject (b) (6) Death due to AML

- 76-year-old female (4L+) received liso-cel on Day 1.
- Day 3 diagnosed with Grade 1 CRS with fever and headache.
- Day 4 CRS worsened to Grade 2 with hypotension and worsening fever; received tocilizumab, dexamethasone, and sodium chloride.
- Day 4 additionally developed NT of aphasia and dyscalculia (related to liso-cel); treated with IV dexamethasone; symptoms resolved the same day.
- Day 29 evaluation with PR (no BM assessment done)
- Day 31 with prolonged Grade 4 thrombocytopenia requiring transfusion.
- Day 72 hospitalized with Grade 3 febrile neutropenia; BM evaluation done due to persistent neutropenia and thrombocytopenia, which revealed AML.

- molecular cytogenetic findings were “consistent with a neoplastic process, myeloid disorder, and secondary malignancy following exposure to environmental toxins or cytotoxic therapy”. Fluorescent in situ hybridization testing revealed loss of 5P15.2 and 5Q31 sequences, loss of 7 centromere and 7Q31 sequences, gain of 3Q26 sequences, and gain of 21Q22.1 (RunX1) sequences (5 to 10 copies). There was no evidence of FL.
- Day 76 Initiated therapy for AML with azacytidine and venetoclax.
- Day 76 RCL testing on blood was negative.
- Day 104 repeat BM assessment consistent with therapy-related AML; transgene testing negative.
- Day 114 subject died of AML.
- BOR: CR.
- A BM biopsy done approximately 7 months prior to infusion of liso-cel demonstrated a normocellular marrow with no morphologic or phenotypic evidence of lymphoma; fluorescent in situ hybridization testing was negative.

Serious Adverse Events

Data:

Table 28: Applicant – Serious TEAEs by SOC and PT (≥ 2% of Subjects) – Liso-cel-Treated Analysis Set

System Organ Class Preferred Term	4L+ FL Cohort 1 N = 59 n (%)	3L FL Cohort 2 N = 48 n (%)	3L+ FL Cohorts 1 + 2 N = 107 n (%)	2L FL Cohort 3 N = 23 n (%)	Total 2L+ FL Cohorts 1, 2, 3 N = 130 n (%)
Subjects With at Least One Serious TEAE	15 (25.4)	13 (27.1)	28 (26.2)	4 (17.4)	32 (24.6)
Immune system disorders	7 (11.9)	4 (8.3)	11 (10.3)	2 (8.7)	13 (10.0)
Cytokine release syndrome	7 (11.9)	4 (8.3)	11 (10.3)	1 (4.3)	12 (9.2)
Nervous system disorders	4 (6.8)	2 (4.2)	6 (5.6)	1 (4.3)	7 (5.4)
Aphasia	4 (6.8)	0	4 (3.7)	1 (4.3)	5 (3.8)
Tremor	2 (3.4)	1 (2.1)	3 (2.8)	0	3 (2.3)
Blood and lymphatic system disorders	3 (5.1)	2 (4.2)	5 (4.7)	0	5 (3.8)
Febrile neutropenia	2 (3.4)	2 (4.2)	4 (3.7)	0	4 (3.1)
General disorders and administration site conditions	1 (1.7)	2 (4.2)	3 (2.8)	1 (4.3)	4 (3.1)
Pyrexia	1 (1.7)	2 (4.2)	3 (2.8)	0	3 (2.3)

Coded using MedDRA version 25.1. A subject is counted only once for multiple events within PT/SOC.
Source: ADSL, ADAE

The Applicant's Position:
The total number of serious TEAEs experienced by subjects receiving 80iso-cel on the FOL-001 Study is comparable to those on other 80iso-cel studies and to other anti CD19 CART cell therapy in patients with FL. The occurrence of serious TEAEs is acceptable in this study population with R/R disease and high-risk features and do not raise any concern for new safety signals.

Adverse Reactions

Data:

Table 29: Applicant – Summary of Adverse Reactions Observed in at Least 10% of the Total per Any Grade – 2L+ FL Population in Study FOL-001

	2L+ FL Total N = 130		
Adverse Reaction	**Any Grade n (%)**	**Serious n (%)**	**Grade ≥ 3 n (%)**
Immune system disorders			
Cytokine release syndrome	75 (57.7)	12 (9.2)	1 (0.8)
Gastrointestinal disorders			
Constipation	26 (20.0)	0	0
Diarrhoea	22 (16.9)	0	0
Nervous system disorders			
Headache	38 (29.2)	0	0
Tremor	18 (13.8)	3 (2.3)	0
General disorders and administration site conditions			
Fatigue[a]	33 (25.4)	0	0
Fever[b]	23 (17.7)	3 (2.3)	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[c]	33 (25.4)	0	0
Infections and infestations			
Infections – pathogen unspecified[d]	18 (13.8)	5 (3.8)	5 (3.8)

[a] Fatigue includes Asthenia, Fatigue.
[b] Fever includes Pyrexia.
[c] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Flank pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity.
[d] Grouped per high-level grouped term.
Source: SCS – ADSL, ADAE

The Applicants Position
The most common nonlaboratory adverse reactions (≥ 20%) were CRS, headache, fatigue, musculoskeletal pain, and constipation (Table 29).

The FDA's Assessment:

Table 30 shows the TEAEs observed in 3L+ FL patients (n=107) with frequencies of ≥10% following treatment with liso-cel. FDA recommends including these in section 6.1

of the USPI. These adverse reactions are reported based on FDA Grouped Terms (see Appendix 17.1. Please note that laboratory abnormalities such as neutropenia, leukopenia, lymphopenia, thrombocytopenia, and anemia are reported separately (under “Lab abnormalities” and are not included in this table).

Table 30. FDA – Summary of Adverse Reactions Observed in at Least 10% of the Total per Any Grade – 3L+ FL Population in Study FOL-001 (N=107)

FDA Group Terms*	All Grade n	All Grade %	Grade ≥3 n	Grade ≥3 %
Cytokine release syndrome	63	59%	1	1%
Headache	30	28%	0	0%
Musculoskeletal pain	30	28%	0	0%
Fatigue	24	22%	0	0%
Constipation	22	21%	0	0%
Fever	21	20%	0	0%
Infection with pathogen unspecified	16	15	5	5%
Diarrhea	16	15%	0	0%
Tremor	16	15%	0	0%

Source: FDA analysis of ADAE data from study FOL-001
*MedDRA preferred terms were grouped as per FDA Grouped term for AE analysis. See Appendix 17.1
Abbreviations; FL, follicular lymphoma

Additionally, FDA recommends including following clinically significant adverse drug reactions occurring in <10% of study subjects (N=107):

Table 31: FDA – Adverse Drug Reactions Occurring in >10% of Subjects in Study FOL-001 (N=107)

Body Organ System FDA Grouped Term*	All Grade %	Grade 3 or Higher %
Blood and lymphatic system disorders	-	-
Febrile neutropenia	5.6	5
Cardiac disorders	-	-
Tachycardia	2.8	0
Eye disorders	-	-
Vision blurred	1.9	0
Gastrointestinal disorders	-	-
Nausea	9.3	0
Abdominal pain	4.7	0
Vomiting	3.7	0
General disorders	-	-
Edema	4.7	0
Chills	3.7	0
Infections and infestations		
Upper respiratory tract infections	7	0
Bacterial infectious disorders	5.6	2
Urinary tract infections	5	1
Viral infectious disorders	1.9	1
Pneumonia	1.9	1
Sepsis	0.9	1

Body Organ System FDA Grouped Term*	All Grade %	Grade 3 or Higher %
Nervous system disorders		
Encephalopathy	7	2
Aphasia	7.5	2
Dizziness	5.6	0
Motor dysfunction	3	0
Ataxia	3.7	0
Neuropathy peripheral	5	0
Psychiatric disorders		
Insomnia	5.6	0
Delirium	4.7	1
Anxiety	1.9	0
Renal and urinary disorders		
Renal disorder	3	0
Renal failure	0.9	0
Respiratory, thoracic and mediastinal disorders		
Cough	6.5	0
Dyspnea	1.9	0
Hypoxia	1.9	1
Vascular disorders		
Hypotension	8.4	0
Hypertension	6	1
Thrombosis	4.7	1
Skin and subcutaneous disorder		
Rash	6.5	1

Source: FDA analysis of ADAE dataset from study FOL-001
*MedDRA preferred terms were grouped as per FDA Grouped term for ADR analysis. See Appendix 17.1

Adverse Events of Special Interest (AESI)

Data:

AESI frequencies are summarized in Table 26.

CRS

The Applicant's Position:

In the Liso-cel-treated Analysis Set, CRS occurred in 57.7% subjects, including Grade ≥ 3 in 0.8% subjects. There were no subjects with fatal CRS. The most common symptoms of CRS (≥ 10%) included pyrexia (56.9%) and hypotension (13.8%) (Table 26, ADSL, ADCRSNT). The median time to CRS onset from the time of liso-cel infusion was 6 days (range: 1 to 17 days). CRS resolved in all subjects; the median time to resolution was 3 days (range: 1 to 10 days).

The FDA's Assessment:

FDA additionally searched ADAE data to identify subjects who were not flagged to have a CRS event, but had one or more CRS symptom, such as fever, hypotension, or hypoxia, not explained by an alternative cause. No such subjects were identified in FDA's review.

Per FDA adjudication, all grade CRS occurred in 59% 3L+ FL subjects including Grade 3 CRS in 1.9%. The median time to CRS onset was 6 days (range: 1 to 17 days). CRS resolved in all subjects, with a median duration of 3 days (range: 1 to 10 days). The most common symptoms of CRS (≥10%) included pyrexia (98.4%) and hypotension (20.6%).

Neurologic Toxicity (specific to the product class)

The Applicant's Position:
In the Liso-cel-treated Analysis Set, iiNT occurred in 15.4% of all subjects, including ≥ Grade 3 in 2.3% subjects. There were no subjects with fatal iiNT (Table 26), ADSL, ADAES). The most common iiNTs by PT were tremor and aphasia (6.9% each) (ADSL, ADAE). The median time to iiNT onset from the time of liso-cel infusion was 8.5 days (range: 4 to 16 days). iiNT resolved in all subjects; the median time to resolution was 3.5 days (range: 1 to 17 days).

The FDA's Assessment:

Out of 107 3L+ FL subjects treated with liso-cel, all grade NT occurred in 15% (16/107) including Grade 3 NT in 3%. The most common manifestations were aphasia, tremor (both 7.5%), and encephalopathy (6.5%). The median time to onset of NT was 8.5 days (range: 4 to 16 days). All NT resolved with a median duration of 4.5 days (range: 1 to 17 days).

Prolonged Cytopenia

The Applicant's Position:
Cytopenias are a recognized complication of CAR T therapy. The rates of Grade ¾ neutropenia and thrombocytopenia seen in Study FOL-001 are consistent with those observed previously with liso-cel. Prolonged cytopenia, defined as ≥ Grade 3 cytopenia at the Day 29 (+/- 2 days) visit based on central laboratory assessments of neutropenia, thrombocytopenia, or anemia, occurred in 29 (22.3%) of all subjects (Table 26).

The FDA's Assessment:

Prolonged cytopenia was defined as 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

The Applicant's Position:
The most common Grade 3-4 infection and infestation in the 2L+ FL Treated Set by PT was infection – pathogen unspecified (SCS – ADSL, ADAE).

The FDA's Assessment:

Infections of any grade occurred in 22% of 3L+ FL patients treated with liso-cel, with Grade 3 or higher occurring in 5.5% of patients. Of these, infections with an unspecified pathogen occurred in 2.8% of patients, followed by bacterial and viral infections in 0.9%. One patient (4L+) developed a fatal case of John Cunningham virus PML 4 months after treatment with liso-cel.

Hypogammaglobulinemia

The Applicant's Position:
Overall, incidences of hypogammaglobulinemia AESIs were low (Table 26) and the majority were mild to moderate in severity (Grade 1-2).

The FDA's Assessment:

FDA agrees with Applicant's assessment.

MAS

The Applicant's Position:
In the 2L+ FL Treated Set, there was one Grade 5 MAS TEAE that was assessed as related to liso-cel. The subject who died within the liso-cel infusion to Day 30 period, experienced Grade 5 MAS/HLH on Day 29, assessed as related to liso-cel treatment by the investigator. The fatal event was preceded by cytomegalovirus reactivation (diagnosed on Day 18) which could have contributed for MAS/HLH.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to above death narrative (#6) for additional information.

IRR

The Applicant's Position:
There were no incidences of IRR.

The FDA's Assessment:

FDA agrees with the Applicant's position.

TLS

The Applicant's Position:
There were no incidences of TLS.

The FDA's Assessment:

FDA agrees with the Applicant's position.

SPM
The Applicant's Position:
SPMs were reported in 4 (3.1%) subjects (Table 26). The frequency of all grade SPMs during the post-treatment emergent period was lower than the background incidence in

this population (9.1% at a mean follow-up of approximately 1.1 years).[56]

The FDA's Assessment:

Seven events of second primary malignancies (SPM) were reported in five 3L+ FL patients treated in FOL-001 study. Two subjects were noted to have two events of SPM.

Table 32. FDA – Second Primary Malignancies in 3L+ FL Subjects Following Treatment With Liso-cel in Study FOL-001

SUBJID	Age/Sex	Cohort	Cancer Type	Start Day After Liso-cel
(b) (6)	76/F	4L+ FL	Acute myeloid leukemia	76
	57/F	4L+ FL	Squamous cell carcinoma	210
	57/F	4L+ FL	Acute myeloid leukemia	359
	56/M	4L+ FL	Squamous cell carcinoma in situ	100
	56/M	4L+ FL	Squamous cell carcinoma in situ	181
	75/M	4L+ FL	Prostate cancer	373
	75/F	3L FL	Rectal cancer	359

Source: FDA analysis of ADSPM data from study FOL-001
Abbreviations; F, female; FL, follicular lymphoma; M, male

Brief narratives are described below for subjects who developed a hematologic SPM:

1) Subject (b) (6) is a 76-year-old female who was treated with liso-cel for R/R FL. The subject developed AML on Day 76 after treatment with liso-cel. BM was tested for presence of CAR transgene and was negative. Per Applicant, the testing for CAR transgene was performed using an ribonucleic acid in-situ hybridization assay in formalin fixed paraffin embedded tissue. The assay included transgene positive and negative controls as well as an internal sample control to ensure the tumor biopsy had adequate ribonucleic acid quality to detect the transgene and prevent false negatives.
   RCL testing done 3 days after diagnosis of AML was negative.
2) Subject (b) (6) is a 57-year-old female who was treated with liso-cel for R/R FL. The subject developed AML with onset on study Day 359. RCL testing done on study day 365 was negative. No tumor tissue/BM was available for testing of CAR transgene.

It should be noted that the risk of T cell malignanices has been recently added as a class safety risk for currently approved CD19 and BCMA-directed CAR T cell therapies, including liso-cel.

Autoimmune Disorders

The Applicant's Position:
No autoimmune disorders were reported in during the treatment-emergent period or post treatment-emergent period.

The FDA's Assessment:

FDA agrees with Applicant's assessment.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:
Given that liso-cel was administered as a single dose for all subjects and follow-up continued for subjects regardless of AEs, this analysis is not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Dose Interruption/Reduction Due to Adverse Effects (if applicable)

The Applicant's Position:
Given that liso-cel was administered as a single dose for all subjects and follow-up continued for subjects regardless of AEs, this analysis is not applicable.

The FDA's Assessment:

FDA agrees with Applicant's assessment.

Laboratory Findings

Table 33: Applicant - Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients Treated with Liso-cel in the Study FOL-001

Laboratory Abnormality	Grade 3 or 4 (%)[b]
Neutrophil count decreased	64
White blood cell decreased	44
Platelet count decreased	12
Anemia	10

Source: SCS - ADLABSUM

The Applicant's Position:
Overall, there were no unexpected or clinically significant laboratory abnormalities occurring following liso-cel infusion.

The FDA's Assessment:

FDA's lab shift analysis was performed on 107 3L+ FL subjects who were treated with liso-cel. The evaluable number for each lab, rather than the total number of safety population, were used as denominator during calculation of frequencies. Our analysis included all subjects with a baseline and at least one post treatment value. Baseline lab values were assessed prior to LDC.

Subjects must have at least one grade worsening on study to be counted in the analysis, and only worse grade lab abnormality was included in our analysis. Of note,

the above method of analyzing lab shift may potentially underestimate the true incidence of lab abnormalities in subjects without a baseline value, especially for labs that are not routinely done at baseline (e.g., uric acid, coagulation profile etc.) Therefore, the review team also included subjects who had missing pretreatment baseline laboratory toxicity grade (BTOXGRN) but had abnormal post treatment toxicity grade (ATOXGRN) as treatment-emergent laboratory abnormality. The analysis of lab abnormalities was limited to a window of 90 days post treatment with LDC/liso-cel.

Table 34 shows the treatment-emergent lab abnormalities observed in adult subjects with R/R FL.

Table 34. FDA - Laboratory Abnormalities Occurring in 3L+ FL Subjects Treated With Liso-cel in Study FOL-001(N=107)

PARAMCD_FDA	Evaluable N	All Grade n	All Grade %	Grade 3 or Higher n	Grade 3 or Higher %
Lymphocyte decreased	107	104	97%	101	94%
White blood cell decreased	107	104	97%	79	74%
Neutrophil decreased	107	98	92%	84	79%
Hemoglobin decreased	107	70	65%	10	9%
Platelet decreased	107	60	56%	18	17%
Calcium decreased	107	48	45%	1	1%
ALT increased	71	35	49%	0	0%
Albumin decreased	106	31	29%	0	0%
Bilirubin increased	78	31	40%	3	4%
AST increased	69	30	43%	0	0%
Sodium decreased	107	27	25%	0	0%
Potassium decreased	107	22	21%	1	1%
Fibrinogen decreased	95	19	20%	0	0%
Creatinine increased	104	17	16%	0	0%
APTT increased	78	16	21%	6	8%
ALP increased	101	11	11%	0	0%
Magnesium decreased	103	11	11%	0	0%
Potassium increased	107	8	7%	0	0%
Calcium increased	107	7	7%	0	0%
Magnesium increased	103	5	5%	1	1%
Sodium increased	107	5	5%	0	0%

Source: FDA Analysis of ADLB data from FOL-001 study
Abbreviations: 3L, having received two lines of prior therapy for the disease under study (third-line treatment); ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FL, follicular lymphoma

Vital Signs

The Applicant's Position:

Abnormal vital signs values, including pyrexia, hypotension, or hypoxia, were mainly associated with events of CRS. Abnormal values were reported as AEs when

considered clinically relevant by the investigator.

The FDA's Assessment:

FDA agrees with Applicant's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:
ECGs were performed at Screening and pre-treatment.

The FDA's Assessment:

FDA agrees with Applicant's position.

Immunogenicity

The Applicant's Position:
See Section 6.

The FDA's Assessment:

See clinical pharmacology reviewer's memo.

90-day Safety Update

The 90-day safety update with a data cutoff date of April 27, 2023, was submitted on February 20, 2024. The new data cutoff date provides an additional 3 months of follow up compared to the primary data cutoff used for the Study FOL-001 (January 27, 2023). At the time of this new data cutoff date, cohorts 1, 2, and 3 had completed enrollment and enrollment was continuing in Cohort 4 (MZL).

No new FL subject was infused with lisocel, all lisocel-treated subjects completed Treatment Emergent Period as of the prior data cutoff date, therefore the frequency of overall TEAEs in the updated 3L+ FL Treated Set remained consistent with the initial safety data.

At the time of the data cut-off for this safety update, 1 new death had occurred, in a subject with 3L FL on study day 628 due to progressive disease. No additional Grade 5 TEAE occurred.
One additional Grade 1 neurologic toxicity occurred. One new event of grade 2 second primary malignancy (mucoepidermoid carcinoma) was reported. The tumor tissue was tested for presence of CAR transgene (method of testing not provided), and the result was negative.

No additional events of CRS, HLH/MAS, infusion related reaction, prolonged cytopenia, serious infections, tumor lysis syndrome, autoimmune disorder or hypogammaglobulinemia were reported.
In conclusion, the 90 days safety update did not show new or clinically significant

safety concerns, compared to the initial safety data submitted with original sBLA submission.

8.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position:
No new potential safety issues were identified as a result of the safety review of liso-cel 100 × 10^6 CAR+ T cells dose.

The FDA's Assessment:

The safety profile of liso-cel in 3L+ FL patients treated in Study FOL-001 was manageable, and as expected with a CD19 CAR T cell therapy.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position: Not applicable

The FDA's Assessment:

Not applicable.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:
Overall TEAE, Grade 3-4 TEAE, and AESI frequencies were similar across subgroups and the overall population and did not reveal any clinically relevant concerns in any subgroup; however, some variability was observed due to the small size of some subgroups.

Results from subgroup analyses of the 2L+ FL group were generally consistent with results from the overall 2L+ FL and 3L+ LBCL plus 2L LBCL Treated Sets.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:
Study GC-LTFU-001 is a LTFU study in all pediatric and adult subjects exposed to gene-modified T-cell therapy in company-sponsored, or company alliance partner-sponsored trials in accordance with Health Authorities' guidance for subjects treated with gene therapy products. Safety data (AEs, deaths) from Study GC-LTFU-001 in subjects who were previously treated with liso-cel was integrated with the parent study in the ISS, per the ISS SAP.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.9 Additional Safety Explorations

Outpatient Setting
The Outpatient Analysis Set includes all subjects in the Liso-cel-treated Analysis Set who are monitored as an outpatient. A subject is considered to be monitored as an outpatient if, following liso-cel administration, the subject is monitored initially as an outpatient, regardless of liso-cel administration setting. In the Outpatient Analysis Set (N = 15; all FL cohorts):

- TEAEs occurred in 15 (100%) subjects overall (ADSL, ADAES).
- AESI occurred in 8 (53.3%) subjects overall, most commonly, CRS (6 [40.0%] subjects) and iiNT (2 [13.3%]) subjects) (ADSL, ADAE, ADCPT).
- 40.0% of subjects experienced CRS, including ≥ Grade 3 in no subjects (ADSL, ADAES, ADAETTE).
  - The median time to CRS onset was 4.0 days (range: 3 to 6 days).
  - CRS resolved in all of subjects, and the median time to resolution was 4.5 days (range: 1 to 8 days).
- 13.3% of subjects experienced iiNT, including ≥ Grade 3 in no subjects (ADSL, ADAES, ADAETTE).
  - The median time to iiNT onset was 7 days (range: 6 to 8 days).
  - iiNT resolved in all subjects, and the median time to resolution was 3.0 days (range: 2 to 4 days).

Pooled Analyses
The safety profile of liso-cel in the FL population was manageable and more favorable than that observed in subjects with LBCL with no new safety signals or new types of clinically important events identified (Table 35).

Table 35: Applicant - Overall Summary of Safety in Pooled Studies

	Number (%) Subjects		
Safety Parameter	**2L+ FL Cohorts 1, 2, 3**	**3L+ LBCL plus 2L LBCL**	**Total**
Liso-cel-treated Analysis Set	***N = 130***	***N = 418***	***N = 548***
Deaths Occurred After First Liso-cel Infusion	12 (9.2)	143 (34.2)	155 (28.3)
Primary Cause of Death			
PD	6 (4.6)	116 (27.8)	122 (22.3)
AE	3 (2.3)	14 (3.3)	17 (3.1)
COVID-19	2 (1.5)	5 (1.2)	7 (1.3)
Unknown	0	4 (1.0)	4 (0.7)

Table 35: Applicant - Overall Summary of Safety in Pooled Studies

Safety Parameter	Number (%) Subjects		
	2L+ FL Cohorts 1, 2, 3	3L+ LBCL plus 2L LBCL	Total
Other	1 (0.8)	4 (1.0)	5 (0.9)
Subjects with any TEAE[a]	128 (98.5)	412 (98.6)	540 (98.5)
Grade ≥ 3	97 (74.6)	337 (80.6)	434 (79.2)
Grade 5	1 (0.8)	13 (3.1)	14 (2.6)
Serious	32 (24.6)	176 (42.1)	208 (38.0)
Liso-cel-related	114 (87.7)	329 (78.7)	443 (80.8)
Liso-cel-related Grade ≥ 3	77 (59.2)	178 (42.6)	255 (46.5)
Liso-cel-related Grade 5	1 (0.8)	8 (1.9)	9 (1.6)
LDC-related	95 (73.1)	352 (84.2)	447 (81.6)
Subjects with any treatment-emergent AESI			
CRS	75 (57.7)	190 (45.5)	265 (48.4)
Grade 1-2	74 (56.9)	177 (42.3)	251 (45.8)
Grade 3-4	1 (0.8)	12 (2.9)	13 (2.4)
iiNT	20 (15.4)	136 (32.5)	156 (28.5)
Grade 1-2	17 (13.1)	94 (22.5)	111 (20.3)
Grade 3-4	3 (2.3)	39 (9.3)	42 (7.7)
IRR	0	3 (0.7)	3 (0.5)
MAS	1 (0.8)	1 (0.2)	2 (0.4)
TLS	0	2 (0.5)	2 (0.4)
Grade ≥ 3 infections	7 (5.4)	50 (12.0)	57 (10.4)
Prolonged cytopenia[b]	29 (22.3)	157 (37.6)	186 (33.9)
Hypogammaglobulinemia	5 (3.8)	47 (11.2)	52 (9.5)
SPM	2 (1.5)	5 (1.2)	7 (1.3)
Autoimmune disorders	0	1 (0.2)	1 (0.2)

[a] TEAEs were defined as AEs occurring from the date of the initial liso-cel infusion (Day 1) through and including 90 days following the final cycle of liso-cel infusion (ie, last dose for Study 017001 which included a 2-dose regimen [DL1D]; first dose for other studies). Any AE occurring after the initiation of subsequent anticancer therapy or liso-cel retreatment.

[b] Prolonged cytopenia is defined as Grade ≥ 3 laboratory results of decreased hemoglobin, decreased neutrophil count, or decreased platelet count at Day 35 (± 6 days) after liso-cel infusion for BCM-003 and at Day 29 (± 2 days) after liso-cel infusion in other studies.

The 3L+ LBCL includes studies 017001 DLBCL Cohort (N = 268) and the 2L LBCL includes studies BCM-003 Arm B and 017006 (N = 150).
Source: ADSL, ADAE, ADCPT

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There have been no confirmed T-cell, or other hematologic, vector-mediated malignancies reported/identified, to date.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:
Liso-cel has not been studied in pregnant subjects. Liso-cel is a novel, experimental product and the effects on the human fetus are unknown. Liso-cel should not be administered to pregnant women.

FCBPs must have a negative pregnancy test prior to LDC and liso-cel administration; FCBP and males must agree to effective contraception for one year after liso-cel infusion largely because of the potential teratogenic effect of LDC with fludarabine and cyclophosphamide, while participating in the study and for an appropriate follow-up period, as described in the study protocols.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth (If applicable)

The Applicant's Position: Not applicable

The FDA's Assessment:

The Study FOL-001 did not enroll pediatric patients. Therefore, this section is not applicable.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
Routine and additional pharmacovigilance activities including periodic comprehensive and detailed reviews, REMS program, LTFU Study (GC-LTFU-001), ongoing registry-based studies, as well as ongoing safety surveillance of all safety data/information received, to date, have not identified a significant safety concern that negatively impacted the current benefit-risk balance of liso-cel in currently approved indications.

Study CA082-1175 is proposed to characterize the long-term safety of liso-cel in R/R FL patients. This study will be based on secondary data that are collected from one or more existing independent registries.

The identified and potential risks of liso-cel are adequately addressed in the current product labeling and through the REMS Program, and no additional risk-minimization measures are considered necessary at this time.

The FDA's Assessment:

The FDA agrees with Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Based upon the established safety profile of liso-cel, it is expected that safety issues can be adequately managed through labeling and routine postmarketing surveillance.

The FDA's Assessment:

Liso-cel has the potential for the serious risk of secondary malignancy due to RCR used in its manufacturing and the potential for insertional mutagenesis. Furthermore, the patients with R/R FL represent a distinct patient population, compared to patients with R/R LBCL or CLL/SLL.

Therefore, a separate LTFU for safety with active surveillance in the R/R FL patient population after treatment with liso-cel will be required. The Applicant has proposed to conduct Study CA082-1175 to characterize the long-term safety of liso-cel in R/R FL. See Section 13 for detail.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:
The totality of the safety data from 130 subjects treated with liso-cel with a median study follow-up of 18.89 months demonstrated a well-tolerated and manageable safety profile which is consistent with that previously reported for the approved indications of 3L+ DBLCL and 2L LBCL.

- No new safety signals or new types of clinically important events were identified with liso-cel monotherapy in R/R 2L+ FL (Study FOL-001)
- The safety events were consistent with previously reported safety findings with liso-cel monotherapy in LBCL (Table 35)
- The types and frequencies of AESIs were as expected since they are known side effects specific to CAR T-cell therapy
- The incidence of Grade > 3 CRS, iiNT, and MAS/HLH was 0.8%, 2.3%, and 0.8%, respectively and considered manageable using the protocol-specified criteria.
- The rates of Grade ≥ 3 infections (5.4%) and prolonged cytopenia (22.3%) were considered acceptable

The FDA's Assessment:

FDA agrees with Applicant's assessment that generally the safety profile from 107 3L+ FL patients from Study FOL-001 is manageable and consistent with that observed in approved 3L+ LBCL, 2L LBCL, and CLL/FL. No new safety signals were identified.

The integrated safety analysis included adverse reaction analysis from a total of 966 patients with various histologies treated with conforming liso-cel (See Table 36).

Table 36**. FDA - Integrated Safety Analysis of Liso-cel**

STUDYID	LBCL[a]	CLL	SLL	MCL	MZL	All
017001	268	-	-	88	-	356
017004	-	109	9	-	-	118
017006	61	-	-	-	-	61
017007	82	-	-	-	-	82
JCAR017-BCM-001	82	-	-	-	-	82
JCAR017-BCM-003	89	-	-	-	-	89
JCAR017-FOL-001	-	-	-	-	48	178
Total	582	109	9	88	48	966

Source: FDA analysis of ISS ADSL dataset
[a] includes 2L LBCL from study , and 3L+ LBCL from study
Abbreviations: CLL, chronic lymphocytic leukemia; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

Basic demographics and disease features

Baseline demographics and disease characteristics of the pooled safety population is shown in Table 37.

Table 37. FDA – Baseline Demographics and Disease Characteristics of the Pooled Safety Population (N=966)

Parameter	Integrated Safety Population N=966
Age (years), median (range)	64 (18-86)
Age <65 years	485 (50)
Age ≥65 years	481 (50)
Sex, n (%)	-
Female	347 (36)
Male	619 (64)
Race, n (%)	-
White	737 (76)
Asian	59 (6)
Black or African American	33 (3)
Others/not reported	137 (15)
Ethnicity, n (%)	-
Non-Hispanic/Latino	784 (81)
Hispanic or Latino	65 (7)
Not reported/Unknown	117 (12)
Screening ECOG, n (%)	-
0	440 (46)
1	496 (51)
2	30 (3)
Bridging therapy, n (%)	577 (60)

Source: FDA analysis of ISS ADSL and ADBASE data

Safety Results

For the purpose of integrated safety analysis, the AEs were analyzed using MedDRA preferred terms with a focus on TEAEs, defined as all AEs occurring or worsening within 90 days after the infusion of liso-cel.

Deaths

A total of 336 deaths occurred out of 966 patients following treatment with liso-cel. The leading cause of death (246/966, 25%) was due to disease progression. The table below summarizes the causes of death:

Table 38. FDA – Analysis of Deaths in the Integrated Safety Analysis Set (N=966)

Parameter	2L and 3L+ DLBCL N=582 n (%)	CLL/SLL N=118 n (%)	FL N=130 n (%)	MCL N=88 n (%)	MZL N=48 n (%)
All deaths	231	44	12	46	3
Disease progression	183	26	6	29	2
Adverse events (AEs)	23	6	3	9	1
Other causes	18	12	3	7	0
Unknown	7	0	0	1	0
Fatal AEs ≤ 30 days after liso-cel infusion	6	3	1	1	0
Fatal AEs > 30 days after liso-cel infusion	17	3	2	8	3

Source: FDA analysis of ISS ADSL dataset
[a] includes 2L LBCL from study 107006 and BCM003; and 3L+ LBCL from study 017001, 017007 and BMC001
Abbreviations: CLL, chronic lymphocytic leukemia; DBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

Table 39 summarizes the most common AEs in the integrated summary of safety.

Table 39. FDA - Analysis of Most Common Adverse Events in Integrated Analysis Set (N=956)

MedDRA PT	3L+ LBCL (n=429) All grade %	3L+ LBCL (n=429) ≥G3 %	2L LBCL (n=148) All grade %	2L LBCL (n=148) ≥G3 %	CLL/SLL (n=118) All grade %	CLL/SLL (n=118) ≥G3 %	FL (n= 127) All grade %	FL (n= 127) ≥G3 %	MCL (n= 88) All grade %	MCL (n= 88) ≥G3 %	MZL (n= 46) All grade %	MZL (n= 46) ≥G3 %
Cytokine release syndrome	44.5	3.3	45.9	1.4	84.7	8.5	58.3	0.8	62.5	1.1	73.9	2.2
Headache	27.7	0.9	23.6	3.4	30.5	0.8	29.1	0.0	22.7	0.0	21.7	2.2
Constipation	22.8	0.2	17.6	1.4	26.3	0.0	19.7	0.0	14.8	0.0	2.2	0.0
Fever	24.7	0.0	15.5	0.0	29.7	0.8	18.9	0.0	18.2	0.0	17.4	0.0
Diarrhea	25.6	1.6	17.6	0.0	30.5	1.7	17.3	0.0	17.0	0.0	28.3	2.2
Fatigue	37.1	1.6	31.8	0.0	36.4	6.8	14.2	0.0	34.1	2.3	19.6	2.2
Tremor	13.5	0.7	12.8	0.7	24.6	1.7	14.2	0.0	11.4	0.0	19.6	0.0
Asthenia	9.3	1.2	7.4	1.4	9.3	0.8	12.6	0.0	1.1	0.0	6.5	2.2
Nausea	32.4	1.2	24.3	0.7	38.1	0.0	9.4	0.0	18.2	2.3	17.4	2.2
Decreased appetite	24.5	2.8	14.9	0.7	25.4	4.2	21.6	4.5	21.6	4.5	13.0	4.3
Vomiting	18.2	0.2	10.1	0.0	14.4	0.0	4.7	0.0	5.7	0.0	6.5	0.0
Dizziness	17.9	0.5	15.5	0.0	26.3	0.0	4.7	0.0	6.8	0.0	13.0	0.0
Cough	17.5	0.0	10.8	0.0	17.8	0.0	7.1	0.0	10.2	0.0	6.5	0.0
Hypotension	16.8	2.8	14.9	1.4	19.5	0.8	7.9	0.0	13.6	0.0	13.0	0.0
Hypogammaglobulinemia	16.6	0.2	7.4	0.7	15.3	2.5	2.4	0.0	11.4	0.0	4.3	2.2
Peripheral edema	15.4	0.7	12.2	0.0	16.1	0.0	4.7	0.0	17.0	1.1	2.2	0.0
Abdominal pain	14.5	1.9	7.4	1.4	18.6	0.0	7.1	0.8	9.1	2.3	6.5	0.0
Febrile neutropenia	12.6	12.4	7.4	7.4	15.3	15.3	6.3	4.7	6.8	5.7	6.5	6.5
Confusional state	12.6	1.9	7.4	2.0	27.1	9.3	2.4	0.8	15.9	2.3	10.9	2.2
Insomnia	12.4	0.2	12.8	0.0	18.6	0.8	5.5	0.0	12.5	0.0	4.3	0.0
Arthralgia	11.2	0.5	10.8	1.4	11.0	0.0	7.9	0.0	11.4	0.0	8.7	0.0
Back pain	11.0	0.9	8.8	0.0	12.7	0.8	7.9	0.8	15.9	1.1	4.3	0.0

MedDRA PT	3L+ LBCL (n=429) All grade %	3L+ LBCL (n=429) ≥G3 %	2L LBCL (n=148) All grade %	2L LBCL (n=148) ≥G3 %	CLL/SLL (n=118) All grade %	CLL/SLL (n=118) ≥G3 %	FL (n= 127) All grade %	FL (n= 127) ≥G3 %	MCL (n= 88) All grade %	MCL (n= 88) ≥G3 %	MZL (n= 46) All grade %	MZL (n= 46) ≥G3 %
Sinus tachycardia	11.0	0.0	6.1	0.0	11.0	0.8	4.8	0.0	10.2	1.1	4.3	0.0
Dyspnea	10.7	0.5	8.8	1.4	20.3	5.9	0.8	0.0	9.1	0.0	8.7	0.0
Anxiety	8.9	0.0	4.7	0.7	14.4	0.8	1.6	0.0	13.6	1.1	6.5	0.0
Chills	8.4	0.0	6.8	0.0	18.6	0.8	3.1	0.0	11.4	0.0	10.9	0.0
Hypertension	8.9	2.6	9.5	4.7	14.4	5.9	4.7	1.6	10.2	3.4	6.5	4.3
Upper resp tract infection	3.5	0.5	2.0	0.0	5.9	0.8	3.1	0.0	10.2	2.3	2.2	0.0
Pain in Extremity	7.7	0.5	6.8	1.4	7.3	0.9	2.4	0.0	10.2	1.1	4.3	0.0
Pleural effusion	5.4	1.2	2.7	0.0	4.2	1.7	1.6	0.0	4.5	0.0	13.0	4.3
COVID-19	2.1	0.9	3.4	2.7	2.5	0.0	3.9	1.6	4.5	4.5	10.9	4.3
Acute kidney injury	4.9	1.4	3.4	0.7	15.3	3.4	0.8	0.0	9.1	0.0	2.2	2.2
Hypoxia	4.4	1.6	2.0	1.4	14.4	10.2	1.6	0.8	3.4	1.1	4.3	2.2
Muscular weakness	5.8	1.6	5.4	2.0	12.7	2.5	1.6	0.0	8.0	0.0	0.0	0.0
Encephalopathy	6.3	3.7	2.7	1.4	11.9	8.5	0.8	0.8	5.7	3.4	0.0	0.0
Dyspepsia	4.4	0.0	2.7	0.0	11.0	0.0	3.1	0.0	1.1	0.0	4.3	0.0
Tumor lysis syndrome	0.5	0.5	0.0	0.0	11.0	11.0	0.0	0.0	2.3	2.3	2.2	0.0
Somnolence	5.8	0.7	3.4	0.7	10.2	3.4	0.8	0.0	5.7	2.3	4.3	0.0

Source: FDA analysis of ISS ADAE dataset
Abbreviations: CLL, chronic lymphocytic leukemia; FL, Follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

For the purpose of labeling, pooled data from currently approved indications (LBCL and CLL/SLL) along with 3L+ FL were analyzed to include in Warnings and Precautions (Section 5). The analyses included a total of 614 patients (418 LBCL patients from Studies BCM-003, 017006, BCM-001, and 017001; 89 CLL/SLL patients from Study 017004; and 107 FL patients from FOL-001).

8.2.12 Integrated Assessment of Effectiveness

The Applicant's Position:
The sBLA for liso-cel in the treatment of adult patients with R/R FL is supported by efficacy results from the large, single arm, multicenter, Phase 2 study, FOL-001. As summarized in Section 8.1.2, data from Study FOL-001 demonstrated, clinically meaningful high ORR and CRR after liso-cel treatment in subjects with R/R FL.

Study FOL-001 evaluated the efficacy of liso-cel, an anti-CD19 CAR T-cell therapy in 124 evaluable subjects with R/R FL. The study enrolled subjects that had received at least one prior line of therapy including those previously treated with combination chemoimmunotherapy consisting of an alkylating agent and anti-CD20 monoclonal antibody. Treated patients had high risk features including those that had POD24 (57.3%), those that were double refractory (62.1%), those with high risk FLIPI score (53.2%), those receiving prior high dose chemotherapy and autologous stem cell transplantation, and those with refractory disease. Some enrolled patients had relapsed or progressed after prior PI3K inhibitor and/or prior R2 therapy. The majority of subjects progressed within 12 months of completion of most recent systemic regimen: 43.5% progressed within 6 months, 11.3% progressed between 6 and 12 months, and 19.4% progressed before regimen completion.

In the 2L+ FL group from Study FOL-001 (N = 124), ORR was 96.0% (95% CI: 90.8, 98.7) and the CRR was 71.8% (95% CI: 63.0, 79.5). With a median follow-up for DOR of 16.66 months, the median DOR was not reached, and 12-month and 18-month rates of continued response were 83.3% and 80.2%, respectively. With a median follow-up for PFS of 17.58 months, the median PFS was not reached, and PFS rates were observed to be high at 12 months (81.9%) and 18 months (77.2%). The median OS was not reached and OS rates were observed to be high at 12 months (92.7%) and 18 months (91.5%). In the 2L+ FL group, ORR and CRR were consistent across all subgroups, including age, sex, number of prior systemic lines of therapy, POD24 subjects, double refractory subjects, prior R2 treated subjects, and subjects that meet the modified GELF criteria.

In the R/R 2L+ FL (POD24 and/or meeting GELF criteria) population, liso-cel monotherapy demonstrated substantially higher ORR in the Liso-cel-treated Efficacy Analysis Set compared to standard treatment options (references for standard of care in SLR).[13] Durability of response was demonstrated by the DOR, PFS, and OS.

The FDA's Assessment:

FDA agrees with Applicant's position. Although the efficacy data in (b) (4) (b) (4) the data is insufficient to support an approval for this population. See Section 8.4.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

Study JCAR017-FOL-001 is a Phase 2 single-arm multicohort, multicenter study which evaluated the efficacy and safety of liso-cel in adults with R/R FL or marginal zone lymphoma. The primary endpoint was ORR, defined as the percentage of subjects with a BOR of CR or PR up to 60 months after JCAR017 infusion per Lugano criteria and as determined by an independent review committee (IRC). The Applicant had a target null ORR of 60%. The statistical testing plan for this single arm trial was descriptive and there were no statistical issues.

8.4 Conclusions and Recommendations

The FDA's Assessment:

Efficacy: The high ORR of 96% (95% CI: 90, 99), with 73% achieving a CR, and a median DOR of not reached (95% CI: 18.04, NE) after all subjects in the primary efficacy population of 94 subjects with relapsed or refractory FL with ≥2 prior lines of systemic therapy, had had the opportunity to be followed up for a minimum of 9 months after first objective response provides evidence of a reasonable likelihood of clinical benefit adequate to support accelerated approval of liso-cel for the indication of adults with R/R FL after 2 or more prior lines of systemic therapy. Of note, the Applicant also sought an indication for (b) (4) the data are insufficient to support an approval for this indication.

Safety: The rates of CRS and NTs were consistent with the known rates in NHL and included serious and life-threatening events. No deaths occurred due to CRS or NT. The treatment algorithms instituted to mitigate these AEs were effective and permitted the benefits of the treatment to outweigh these risks. No new safety signals were identified in this study. Additionally, T cell malignancies have occurred following treatment of hematologic malignancies with B-cell maturation agent- and CD19-directed genetically modified autologous T cell immunotherapies, including liso-cel. Therefore, a

15-year LTFU study to monitor for long-term safety including secondary malignancies, is required.
To ensure safety, the following measures should be followed:

1) The current USPI includes a boxed warning for CRS, NTs, and T cell malignancies.
2) REMS with ETASU of liso-cel.
3) A safety PMR study for 15-year long-term follow-up of FL patients treated with liso-cel for risk of secondary malignancies.

In summary, the Study JCAR017-FOL-001 represents an adequate and well-controlled trial. The high magnitude of benefit based on response rate and DOR in the proposed population forms the basis for substantial evidence of effectiveness in the context of an acceptable safety profile, and therefore supports an accelerated approval of liso-cel in treatment of adults with R/R FL after 2 or more prior lines of systemic therapy. Additionally, previous adequate and well-controlled trials of liso-cel have demonstrated evidence of effectiveness in treatment of related CD19 expressing hematologic malignancies (LBCL and CLL/SLL), forming the basis for approval for those indications. Given the indolent nature of FL, which may afford the potential for prolonged survival and multiple therapeutic interventions, the response rates seen with liso-cel in the intended patient population along with the degree of follow-up associated with the durability of response, the review team recommends an accelerated approval with a requirement for a confirmatory study. Continued approval for this indication may be contingent upon verification and description of clinical benefit.

For verification of clinical benefit, two options were considered 1) a randomized trial with a time to event endpoint such as PFS or OS or 2) additional DOR follow-up of the current patients in Study FOL-001. The additional follow-up of at least 24 months for DOR in Study FOL-001 was selected to verify the clinical benefit of liso-cel in the indicated population based on the following rationale:

- 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 NHL, including one randomized controlled trial.
- There is no established standard of care for patients with R/R FL receiving third line treatment and beyond, however there are multiple therapeutic interventions that may be considered.
- In patients with R/R FL, outcome with each successive line of therapy is worse, 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 third line treatment of R/R FL may impact the feasibility of accruing and completing a randomized trial.

X X

Primary Clinical Reviewer Clinical Team Leader

X

MORE Team Lead

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Advisory committee meeting was not conducted for this submission. No external consultations were required.

10 Pediatrics

The Applicant's Position:
Liso-cel for treatment of FL was granted ODD (US ODD # 17-6005 07 Sep 2017). Per the PREA and 21 CFR 314.55 (d), it is exempt from pediatric study requirements for that indication.

The FDA's Assessment:

FDA agrees with Applicant's assessment. Study JCAR017-FOL-001 did not enroll or treat pediatric patients. This is a supplemental BLA application seeking registration of liso-cel for the indication of adults with R/R FL after 2 or more prior lines of systemic therapy. Liso-cel has orphan drug designation for treatment of FL. Therefore, the application is exempt from Pediatric Research Equity Act requirements for this indication.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1. Indications and Usage	BREYANZI is indicated for the treatment of adult patients with follicular lymphoma who have: (1) (b) (4) or (2) Relapsed or refractory disease after 2 or more lines of systemic therapy This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).	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. This indication is approved under accelerated approval based on response rate and duration of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).
2. Dosage and Administration	For FL the dose is 90 to 110 × 10^6 CAR-positive viable T cells	Agree with Applicant's proposal
5. Warnings and Precautions	• CRS (5.1) • Neurologic toxicities (5.2) • Breyanzi REMS (5.3) • Serious infections (5.5) • Prolonged cytopenias (5.6) • Hypogammaglobulinemia (5.7)	FDA recommends revising W&P subsections to include pooled data from approved indications in concise fashion. Additionally, the W& P in current USPI include following: • Hypersensitivity reactions (5.4) • Secondary Malignancies (5.8) • Effects on ability to drive and use machines (5.9) • Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) (5.10)
6.1 Clinical Trials Experience (TRANSCEND-FL)	The most common nonlaboratory adverse reactions (≥ 20%) in FL are CRS, headache, fatigue, musculoskeletal pain, and constipation. The most common Grade 3-4 laboratory abnormalities include neutrophil count decreased, white blood cell decreased, platelet count decreased, and hemoglobin decreased.	FDA recommends the revision of content in Section 6.1: • To include adverse reactions in primary safety analysis population (n=107) • To include lab shift abnormalities using preLDC lab as baseline.
6.2 Immunogenicity	Pre-existing ATA and treatment-induced or treatment boosted ATA details added for FL.	FDA recommends moving immunogenicity to Section 12.
8.5 Geriatric Use	Addition of FL details added.	FDA agrees

14.2 Clinical studies, R/R Follicular Lymphoma	Addition of TRANSCEND-FL clinical study.	FDA recommends revising this section to include efficacy data from primary efficacy evaluable population (n=94)

Of note, Section 5 Warnings and Precautions of the USPI has been reorganized to include pooled data from all currently approved indications (N=614 patients). This includes 418 LBCL patients from studies BCM-003, 017006, BCM-001 and 017001; 89 CLL/SLL patients from study 017004; and 107 3L+ FL patients from FOL-001.

The Applicant's Position:

The clinical data provided in this sBLA demonstrate the clinical benefit and safety of the use of liso-cel for the treatment of adult patients with FL who have:

1 (b) (4)

2 R/R disease after 2 or more lines of systemic therapy

The FDA's Assessment:

As discussed in Section 8.4, the clinical data submitted in this BLA demonstrate favorable benefit-risk supporting accelerated approval of liso-cel for indication of adults with R/R FL after 2 or more prior lines of systemic therapy. However, the evidence is insufficient to support the proposed indication of (b) (4)
(b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

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

Refer to the Office of Biostatistics and Pharmacovigilance review memo for details.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

1) Confirmatory Study:

The clinical review team recommends accelerated approval of liso-cel for the treatment of adult patients with R/R FL after 2 or more prior lines of systemic therapy. Additional data are needed to confirm the clinical benefit for consideration of conversion to traditional approval. Therefore, we recommend the PMR as outlined below:

- Collect and submit the final report, including datasets from the TRANSCEND FL clinical trial (NCT04245839) to verify and describe the clinical benefit of liso-cel in adult patients with relapsed or refractory FL after 2 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.

The Applicant has proposed following timelines:

- Final Protocol Submission: August 15, 2022 (Date of submission of Study JCAR017-FOL-001 protocol Amendment 1 to IND 016506)
- Study/Trial Completion: May 31, 2025
- Final Report Submission: August 31, 2025

The Applicant notes that the final Protocol Submission date reflects the date of submission of Study JCAR017-FOL-001 Protocol Amendment 2 to IND 016506. Overall, the Applicant's proposed timelines for collection and submission of 24 months DOR data appear reasonable.

2) Post-marketing registry study (CA082-1175):

The pharmacovigilance plan requires a long-term, prospective, non-interventional PMR registry in subjects treated with liso-cel. Currently, the Applicant is conducting an ongoing observation registry study including 1700 LBCL and 300 CLL/SLL patients to inform short term toxicity, documenting AEs and long-term follow-up evaluation of secondary malignancies. The Applicant has agreed to include 300 patients with FL and follow up for 15 years.

The Applicant has proposed the following milestones:

- Final protocol submission: August 1, 2024
- Study completion date: August 31, 2044
- Final report submission: August 31, 2045

14 Chief, Malignant Hematology Branch

X

15 Oncology Center of Excellence (OCE) Signatory

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

16 Division Director (Division of Clinical Evaluation Hematology)

X

17 Appendices

17.1 FDA Grouped Terms

Table 40. FDA - Grouped Terms Used to Analyze Adverse Drug Reactions.

Grouped Terms	Preferred Terms
Abdominal pain	Abdominal pain Abdominal pain upper
Aphasia	Aphasia Speech disorder
Ataxia	Ataxia Balance disorder Gait disturbance
Bacterial infection	Device related bacteriemia
Arrhythmia	Conduction disorder Bradycardia
Chest discomfort	Chest discomfort Non-cardiac chest pain Palpitations Musculoskeletal chest pain
Cyst	Cyst Synovial cyst
Delirium	Agitation Hallucination, visual Irritability Disorientation
Diarrhea	Diarrhoea
Dyscalculia	Calculation error Trouble counting backwards
Dizziness	Dizziness Syncope
Dyspnea	Dyspnoea Dyspnoea exertional
Edema	Oedema peripheral Peripheral swelling
Encephalopathy	Cognitive disorder Disturbance in attention Confusional state Depressed level of consciousness Mental impairment Disorientation Encephalopathy Lethargy Memory impairment
Eye disorder	Vision blurred Dry eye Eye pain Chalazion

Grouped Terms	Preferred Terms
Fatigue	Asthenia Fatigue Somnolence
Fungal infection	Fungal disease carrier
Gastrointestinal disorder	Large intestinal obstruction Dyspepsia Flatulence Intestinal transit time abnormal
Gastroenteritis	Campylobacter gastroenteritis
Hemorrhage	Epistaxis Haemoptysis Vascular access site haemorrhage Vascular access site haematoma Contusion
Hypertension	Hypertension Blood pressure increased
Infections - pathogen unspecified	Grouped per high-level group term
Motor dysfunction	Muscle contracture Muscular weakness Dysarthria Fine motor function dysfunction
Musculoskeletal pain	Arthralgia Back pain Bone pain Muscle spasms Flank pain Pain in extremity Myalgia Musculoskeletal pain Neck pain Muscle tightness Groin pain Tendonitis Ligament sprain
Neuropathy peripheral	Carpel tunnel syndrome Peripheral sensory neuropathy Hyperesthesia Paraesthesia Tinnitus
Oral pain	Mucosal inflammation Stomatitis Odynophagia Oropharyngeal pain Toothache Temporomandibular joint syndrome
Pain	Discomfort Pain Pain of skin

Grouped Terms	Preferred Terms
Rash	Rash Urticaria Hyperkeratosis Petechiae Dermatitis contact Catheter site rash
Renal disorder	Cystitis noninfective Reb blood cells urine positive Pollakiuria
Secondary malignancy	Hypergammaglobulinemia benign monoclonal Acute myeloid leukemia
Sepsis	Escherichia sepsis
Skin disorder	Alopecia Dry skin Flushing Hyperhidrosis Pruritis Inflammation
Tachycardia	Sinus tachycardia Tachycardia
Thrombosis	Axillary vein thrombosis Device related thrombosis Subclavian vein thrombosis Embolism
Upper respiratory tract infection	Nasopharyngitis Pharyngitis Sinusitis Nasal congestion Rhinorrhoea Upper respiratory tract infection
Urinary tract infection	Cystitis Escherichia urinary tract infection Urinary tract infection bacterial Urinary tract infection
Viral infection	COVID-19 pneumonia COVID-19 SARS-CoV-2 test positive Rhinovirus infection

17.2 Definition of FDA Algorithm and IRC Charter

Table 41. FDA - Key Differences Between Response Evaluation per FDA Algorithm Versus IRC Charter

Terminology	FDA algorithm	IRC charter
Response evaluation	IRC Procedures Document using the Lugano Classification	IRC charter using a modified Lugano Classification (using PET scan instead of BMB for lymphomatous bone marrow involvement)
Censoring rules	FDA censoring rules for DOR and PFS	EMA censoring rules for DOR and PFS
Per-protocol analyses	Sensitivity analyses; referred as "FDA criteria" in the statistical outputs	Primary analyses; referred as "IRC assessment" in the statistical outputs

Source: JCAR017-FOL001 Study Interim clinical study report
Abbreviations: BMB, bone marrow biopsy; DOR, duration of response; EMA, European Medicines Agency; IRC, Independent Review Committee; PFS, progression free survival

17.3 Event and Censoring Rules for DOR and PFS in Study FOL-001

Table 42. FDA - Event and Censoring Rules for DOR and PFS in Study FOL-001

	FDA Censoring Rules		EMA Censoring Rules	
Scenario	Censor/Event	Date	Censor/Event	Date
Death or documented PD	Event	Documented PD or death date, whichever is earlier	Event	Documented PD or death date, whichever is earlier
Start new anti-lymphoma therapy before PD/death[a]	Censor	Last adequate assessment date with no evidence of PD before starting new subsequent anti-lymphoma therapy	Event	Documented PD or death date, whichever is earlier
No documented PD and no death	Censor	Last adequate assessment date with evidence of no PD	Censor	Last adequate assessment date with evidence of no PD

[a] Both allo- and auto-HSCT are considered as a new antineoplastic therapy.

Source: JCAR017-FOL-001 Statistical Analysis Plan
Abbreviations: DOR, duration of response; EMA, European Medicines Agency; PD, progressive disease; PFS, progression free survival

17.4 References

The Applicant's References: See Section 17.6.

FDA References

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17.5 Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the FOL-001 Study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators.*

The FDA's Assessment:

Financial disclosure information was provided for 568 investigators and sub-investigators, including 4 who were noted to have disclosable financial interests, and 1 who was a Sponsor employee. The Applicant provided a description of steps that have been taken to minimize potential bias from these reported financial interests. The table below has been confirmed by the FDA.

The review of the financial disclosures did not identify issues that could unfavorably impact the clinical review of this submission.

Covered Clinical Study (Name and/or Number):* JCAR-017-FOL-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 568		
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): 4		
If there are investigators with disclosable financial interests/arrangements, identify the		

<table>
<tr><td colspan="3">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: 3

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in study: 1

Sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☒</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☒</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☒</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

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