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Supplemental 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)	125714/644
Priority or Standard	Priority
Submit Date(s)	6/5/2025
Received Date(s)	6/5/2025
PDUFA Goal Date	12/5/2025
Division/Office	Office of Therapeutic Products
Review Completion Date	12/1/2025
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 relapsed or refractory marginal zone lymphoma (MZL) who have received 2 or more lines of systemic therapy
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received 2 or more lines of systemic therapy

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Response assessment occurred per the IRC charter dated September 11, 2022 which indicated that radiographic assessment would occur with two different radiologists independently reading each study subject. If there was no discordance, results from the first radiology read would be used. If there was discordance, adjudication would be performed by a radiologist who was not involved in the primary radiology review and who was blinded to the identity of the two primary readers. The adjudicator reviewed but did not reread the two primary reads and would choose the read felt to most accurately represent the prespecified adjudication variables, i.e. CT and CNS Best Response, CT

and CNS Date of Progression, and CT and CNS Date of First Response. SAP version 4 dated May 14, 2024 added the following analyses relevant to the 3L MZL population: Table 24 below summarizes the efficacy data for 66 efficacy evaluable MZL subjects who met duration of follow up criteria (i.e. at least 9 months of DOR follow up) and for 77 leukapheresed patients using IRC assessed response per Lugano criteria. FDA Preliminary Meeting Comments generated 10/10/2024 (CRMTS 20603) indicated that the primary analysis should take place when at least 60 patients had been followed for DOR for a minimum of 12 months after first response as assessed by IRC. However, the FDA will accept at least 9 months of DOR follow up in this indolent lymphoma. DOR follow up begins at the time of first objective disease response, not the first disease assessment. The ORR was high in both the primary efficacy population and the leukapheresed population, albeit slightly lower in the leukapheresed population. The ORR is favorable in R/R MZL and is supported by duration of response and safety as described below and in section 8.2. Table 23: FDA - Response Rates in Subjects with R/R MZL Treated with Liso-cel in Study FOL-001 63
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OCE=Oncology Center of Excellence
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Glossary

Abbreviation	Definition
1L	First-line
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
ATC	Anatomical therapeutic chemical
AUC	Area under the blood concentration-time curve
Axi-cel	Axicabtagene ciloleucel
BB-IND	Biological-based Investigational New Drug (application)
BLA	Biologics License Application
BMB	Bone marrow biopsy
BMS	Bristol-Myers Squibb Company
BOR	Best overall response
B-R	Bendamustine/rituximab
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
CK1	Casein kinase 1
CLL	Chronic lymphocytic leukemia
Cmax	Maximum observed blood concentration
COA	Clinical outcomes assessment
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
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EMZL	Extranodal marginal zone lymphoma
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
EU	European Union
FACT-LymS	Functionality Assessment of Cancer Therapy Lymphoma Subscale
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FL3B	Follicular lymphoma grade 3B
GBDS	Global Biometric and Data Sciences
GCP	Good clinical practice
GCSF	Granulocyte colony-stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
GHS	Global health score
HGBCL	High-grade B-cell lymphoma
HLH	Hemophagocytic lymphohistiocytosis
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
ICH	International Council on Harmonisation

Abbreviation	Definition
ICU	Intensive care unit
ID	Identification
IgG	Immunoglobulin G
iiNT	Investigator-identified neurologic toxicity
IL	Interleukin
IND	Investigational New Drug
iNHL	Indolent non-Hodgkin lymphoma
IVIG	Intravenous immunoglobulin
IPD	Important protocol deviation
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISA	Insertion site analysis
ISS	Integrated Summary of Safety
ITT	Intent 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
LVEF	Left ventricular ejection fraction
MALT	Mucosa-associated lymphoid tissue
MAS	Macrophage activation syndrome
Max	Maximum
MCL	Mantle cell lymphoma
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRD	Minimum residual disease
MRI	Magnetic resonance imaging
MZL	Marginal zone lymphoma
NA	Not applicable (not reached)
NCI	National Cancer Institute
NCP	Nonconforming product
NHL	Non-Hodgkin lymphoma
NMSC	Non-melanoma skin cancer
NMZL	Nodal marginal zone lymphoma
NOS	Not otherwise specified
NT	Neurotoxicity
ODD	Orphan Drug Designation
ORR	Overall response rate
OS	Overall survival
PAS	Prior approval supplement
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 B Cell Lymphoma
PMR	Partial metabolic response
POD24	Progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PRR	Partial response rate
PT	Preferred term
PVS	Persistence vector sequence
QoL	Quality of life
R2	Rituximab and lenalidomide
RCL	Replication-competent lentivirus
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
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sBLA	Supplemental Biologics License Application
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMQ	Standardized MedDRA query
SMZL	Splenic marginal zone lymphoma
SN	Sequence number
SOC	System organ class
SPD	Sum of the products of the perpendicular diameters
SPM	Second primary malignancy
T-cell	T-lymphocyte
TCL	T-cell lymphoma
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
Tmax	Time of maximum observed blood concentration
ULN	Upper limit normal
US	United States
WHO	World Health Organization
VAS	Visual analog scale(s)

1 Executive Summary

1.1. Product Introduction

Lisocabtagene maraleucel (Breyazi), hereafter referred to as 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 an anti-CD19 single chain variable fragment (scFv), an IgG4 hinge region, a CD28 transmembrane domain, a 4-1BB co-stimulatory domain, and a CD3 zeta activation domain.

Liso-cel currently has traditional approval in adult patients with the following aggressive histologies:

- large B cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; relapsed or refractory disease after 2 or more lines of systemic therapy
- relapsed or refractory mantle cell lymphoma (MCL) who received at least 2 prior lines of systemic therapy, including a Bruton tyrosine kinase (BTK) inhibitor.

Liso-cel currently has accelerated approval in adult patients with the following indolent histologies:

- relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor
- relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy

The Applicant's new proposed indication for this product is for the treatment of adult patients with relapsed or refractory MZL after two or more lines of systemic therapy. In support of this application, the Applicant submitted safety and efficacy data from cohort 4 of the clinical study, JCAR-FOL-001.

The review team recommends a traditional approval of liso-cel for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) after two or more lines of systemic therapy.

The recommended dose in MZL is a single intravenous infusion of 90 to 110 X 10^6 CAR-positive viable T cells, preceded by fludarabine and cyclophosphamide for lymphodepletion. A single dose of liso-cel contains CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the traditional approval of liso-cel is based on efficacy and safety data from JCAR-FOL-001 Cohort 4.

JCAR-FOL-001 Cohort 4 is a global, phase 2, open-label, single arm trial that evaluated a single infusion of liso-cel, preceded by lymphodepleting chemotherapy, for the treatment of subjects with relapsed or refractory MZL who had previously been treated with two or more lines of systemic therapy, including an anti-CD20 monoclonal antibody (mAb) combined with an alkylating agent or who had relapsed after hematopoietic stem cell transplant. The primary endpoint by overall response rate (ORR) defined as the percentage of subjects with a best overall response of complete response (CR) or partial response (PR), as confirmed by IRC per Lugano classification (Cheson 2014). Enrolled patients were not required to have an indication for systemic treatment, and initiation of treatment was per investigator assessment. In total, 77 patients were enrolled (i.e. underwent leukapheresis), and 67 patients received liso-cel. These subjects constituted the safety analysis set.

Sixty-six (66) patients were included in the primary efficacy analysis. The primary efficacy population comprises patients with MZL after 2 or more prior lines of systemic therapy with measurable disease at baseline and have had at least nine months of follow up for duration of response measured from the date of their first disease response to the data cutoff date of November 29, 2024. Among all study subjects, 10 subjects did not receive lisocabtagene maraleucel for the following reasons: administration of nonconforming product in two patients, progressive disease in four patients, failure to meet treatment criteria in three patients including one with cardiovascular complications, and suicide.

Efficacy:

On intention to treat (ITT) analysis, of the 77 subjects with relapsed or refractory MZL who underwent leukapheresis, the ORR was 84.4% (95% CI: 74.4, 91.7) with a CR rate of 55.8% (95% CI: 44.1, 67.2). Among 66 primary efficacy population, the ORR was 95.5% (95% confidence interval [CI]: 87.29, 99.05) with a CR rate of 62.1% (95% CI: 49.3, 73.8). With an estimated median follow up from date of first response of 21.59 months (95% confidence interval [CI]: 17.28, 22.77), the median duration of response was not reached (95% confidence interval [CI]: 25.59, NR). The one year and two year rates of continued remission were 96.7 (95% confidence interval [CI] 87.3, 99.2) and 90.1 [95% confidence interval [CI] 73.1, 96.6).

The ORR of 95.5% observed in FOL-001 is higher than the ORRs seen with approved therapies which range from 51-74% for therapies with regular approval. The CR rate of 62.1% observed in FOL-001 is also higher than the CRR seen with approved products (13-29%). The treatment effect was durable in subjects with R/R MZL although long-term durability in an indolent disease that has a median overall survival of 10 years with current treatment optionsremains uncertain. The magnitude of the treatment effect, however, appears consistent across exploratory subgroup analyses of the three marginal zone lymphoma subtypes despite extranodal MZL and splenic MZL having limited representation in the efficacy population.

Considering the therapies available to patients with relapsed or refractory MZL who have received at least 2 prior therapies, the clinical review team assesses a favorable benefit-risk profile of liso-cel in the indicated population. Clinical benefit in an indolent lymphoma ultimately rests on demonstration of improved progression-free survival (PFS) and/or overall survival (OS). Although ORR is an intermediate clinical endpoint likely to predict clinical benefit in this disease and therefore an endpoint in support of accelerated approval, the FDA considered whether it was reasonable to apply regulatory flexibility in providing traditional approval. In doing so, the FDA considered the a) magnitude of the ORR in the ITT (leukapheresed) population following b) a single treatment with liso-cel in Study FOL-001 c) supported by treatment free durability of both complete and partial responses with a d) median follow up period for response of 21.5 months e) in a study population where 35% of subjects had either progression of disease within 2 years from diagnosis to support a traditional approval.

Safety:

1. FOL-001 was the primary source of safety data and included a total of 67 subjects who were treated with liso-cel. Grade 3 or higher adverse reactions occurred in 59 subjects (88%). Adverse events of special interest included the following: cytokine release syndrome (51 subjects; 76%; grade 3 in 4.5%), investigator-identified neurotoxicity (22 subjects; 33%; grade 3 in 4.5%), infusion related hypersensitivity reaction (one subject; 1.5%; grade 1); hemophagocytic lymphohistiocytosis (3 subjects; 4.5%; all grade 3); tumor lysis syndrome (one subject; 1.5%; grade 1);

hypogammaglobulinemia (4.5%); grade 3 and greater infections (6 subjects; 9%); second primary malignancies (8 subjects; 12%; 4.5% grade 3 or greater); and prolonged cytopenias (65 subjects; 97%; 40% grade 3 or higher), serious adverse events (SAEs) occurred in 39% of patients with grade 3 and greater SAEs occurring in 21% of patients. Two subjects had fatal adverse reactions which included: one patient who developed a T cell lymphoma at day 32, negative on insertional site analysis (ISA) and one patient who developed neutropenic sepsis at day 47 with multiple unresolved concurrent neurologic toxicities at the time of death. There was no evidence of insertional mutagenesis reported in the sBLA.

The life-threatening and fatal adverse reactions warrant the boxed warning that is already in place in the USPI for CRS, neurotoxicity, and T cell malignancies. To inform prescribers to clinically significant serious, life-threatening, and fatal adverse reactions associated with liso-cel, the following events will remain in the Warnings and Precautions section of the label: hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia, and secondary malignancies. The most common adverse reaction in the label remains CRS.

Long-term safety after treatment with liso-cel will be addressed with a PMR long-term follow up registry study that will extend follow up to 15 years. The postmarketing multicenter, prospective, observational study will assess the long-term safety of liso-cel and the risk of secondary malignancies occurring after treatment with liso-cel. The study will include at least 300 adult patients with relapsed or refractory MZL. The enrolled patients will be followed for 15 years after the product administration.

Conclusion:

The clinical review team recommends granting a traditional approval of liso-cel for the following indication:

Lisocabtagene maraleucel is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma after two or more lines of systemic therapy.

This recommendation is based on the efficacy of liso-cel from Study FOL-001 Cohort 4, an adequate and well controlled study that provides substantial evidence of effectiveness, based on overall response rate and durability of response further supported by complete response rate and a tolerable safety profile, in patients with relapsed or refractory MZL. The substantial evidence of effectiveness from Study FOL-001 Cohort 4 is further substantiated by the confirmatory evidence of activity of liso-cel in MZL based on 1) a clear mechanistic rationale and 2) the fact that liso-cel has been approved for treatment of other related CD19 expressing hematologic malignancies based on other adequate and well controlled studies.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment of liso-cel in adult patients with relapsed or refractory MZL after 2 or more prior lines of systemic therapy is favorable.

Efficacy:

Efficacy of lisocabtagene maraleucel is based on the results of Study FOL-001, a global, open-label, phase 2, single arm trial in 77 patients with relapsed or refractory marginal zone lymphoma who received at least two prior therapies (including at least one line of combination systemic therapy or therapy with an anti-CD20 antibody and an alkylating agent) or patients who have relapsed after HSCT. An indication for systemic treatment was not required for study enrollment. Treatment was initiated per investigator assessment.

Patients received fludarabine 30 mg/m2/day and cyclophosphamide 300 mg/m2/day lymphodepleting chemotherapy for 3 days prior to lisocabtagene maraleucel infusion on day 1 at a dose of 100 X 10^{-6} CAR-positive T cells. Efficacy was established on the basis of overall response rate (ORR) as assessed by CT using the Lugano Classification (Cheson 2014). In the ITT population (n=77), the overall response rate of 84.4% [95% CI: 74.4, 91.7], with 55.8% [95% CI: 44.1, 67.2] achieving a complete response. Among the 66 patients in the efficacy evaluable population, the ORR was 95.5% [95% CI: 87.29, 99.05] with a CR rate of 62.1% [95% CI: 49.3, 73.8]. With an estimated median follow up from the date of first response of 21.59 months [95% CI: 17.28, 22.77], the median duration of response was not reached [95% CI: 25.59, NR]. The one year and two-year rates of continued remission were 96.7 [95% CI: 87.3, 99.2] and 90.1 [95% CI: 73.1, 96.6).

Safety

The safety profile of lisocabtagene maraleucel was supported by an analysis of 67 patients with relapsed or refractory MZL. The most common adverse events (>20%) were cytokine release syndrome, fatigue, diarrhea, musculoskeletal pain, encephalopathy, headache, and tremor. The most common grade 3 to 4 laboratory abnormalities (>10%) were: lymphocyte count decreased (99%), neutrophil count decreased (84%), white blood cell count decreased (84%), platelet count decreased (28%), and hemoglobin decreased (25%). Serious adverse events occurred in 39% of patients, most often due to cytokine release syndrome (19.4%), encephalopathy (10.45%), aphasia (7.46%), tremor (4.5%), sepsis (4.5%), and 3% each of dizziness, delirium, transient ischemic attack, and infusion related hypersensitivity. Adverse events of special interest included the following: cytokine release syndrome

(76%), investigator-identified neurotoxicity (33%), infusion related hypersensitivity reaction (1.5%); hemophagocytic lymphohistiocytosis (4.5%); tumor lysis syndrome (1.5%); hypogammaglobulinemia (4.5%); grade 3 and greater infections (9%); second primary malignancies (12%); and prolonged cytopenias (97%).

Benefit-Risk:
Lisocabtagene maraleucel has an overall favorable benefit-risk in patients with relapsed or refractory marginal zone lymphoma after two or more lines of systemic therapy. In the 66 patients with relapsed or refractory FL enrolled in Study FOL-001, the median age was 63 years (range: 37, 81), 45% were 65 years or older, 58% were male, and 58% were White. A total of 84% had stage 3-4 disease, 21% had bulky disease, and all patients had an ECOG performance status of 0 or 1. The median number of prior therapies was 3 (range: 2, 12). A total of 35% had POD24 disease and 10% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy. 23% had received prior rituximab and lenalidomide therapy and 14% had received prior Zanubrutinib.

In this population, the overall response rate of 95.5%, with 62.1% achieving complete response with durability and a tolerable safety profile provides a meaningful clinical benefit and a favorable benefit-risk evaluation. The ORR of 95.5% observed in FOL-001 exceeds the ORRs seen with available therapies which range from 51-74% for therapies with regular approval. The CR rate of 62.1% observed in Study FOL-001 also exceeds the CRR seen with approved products (13-29%).

Thus, the benefit-risk of lisocabtagene maraleucel is deemed favorable to support approval for the following indication:
- Treatment of adult patients with relapsed or refractory marginal zone lymphoma after two or more lines of systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Marginal zone lymphoma (MZL) is a heterogeneous group of indolent lymphomas composed of extranodal MZL of mucosa-associated lymphoid tissue (EMZL), nodal MZL (NMZL), and splenic MZL (SMZL). • Repeated relapses are common, and treatment is individualized based on the presence or absence of histologic transformation, stage and extent of disease, symptoms, organ involvement, number and type of prior treatments, duration of remission, and the patient's performance status. • The median overall survival among patients with marginal zone lymphoma is 10 years. • Survival in the setting of progression of disease within 2 years after initial treatment is reduced (i.e. 3-5 years) and is the strongest prognostic biomarker of reduced survival.	• Relapsed and refractory marginal zone lymphoma is a serious and life-threatening disease.
Current Treatment Options	• Active surveillance is common for patients with advanced-stage disease who are asymptomatic. • Criteria for initiating treatment include progressive lymphadenopathy, organomegaly, cytopenias, and B symptoms. • Currently approved treatment options in the relapsed and refractory setting include lenalidomide for adult patients with previously treated MZL in combination with a rituximab product and bendamustine for patients with indolent B-cell NHL that has progressed during or within six months of treatment with a rituximab or a rituximab-containing regimen. Zanubrutinib is currently approved under accelerated approval for adult patients who have received at least one anti-CD20 based regimen.	• New treatments are needed for patients with relapsed or refractory marginal zone lymphoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Study FOL-001 was a global, open-label, phase 2, single arm trial. The trial enrolled 77 patients; 66 patients were treated with conforming liso-cel at intended dose, and had at least 9 months of follow up for duration of response. Initiation of systemic treatment was per investigator assessment. • Patients received lymphodepleting chemotherapy followed by a single lisocabtagene maraleucel infusion at a dose of 100 X 10^{-6} CAR-positive T cells. • Overall response rate per independent review committee in the ITT population was 84.4% [95% CI: 74.4, 91.7], with 55.8% [95% CI: 44.1, 67.2] achieving a complete response. ORR in the 66 treated patients was 95.5% (95% confidence interval [CI]: 87.29, 99.05) with a CR rate of 62.1% (95% CI: 49.3, 73.8). • With an estimated median follow up from date of first response of 21.59 months (95% confidence interval [CI]: 17.28, 22.77), the median duration of response was not reached (95% confidence interval [CI]: 25.59, NR).	• High ORR with durability, further supported by high CRR, indicate clinically meaningful activity of liso-cel in patients with relapsed or refractory marginal zone lymphoma who have received at least two or more lines of systemic therapy.
Risk and Risk Management	• The safety profile of lisocabtagene maraleucel was supported by an analysis of 67 patients with relapsed or refractory MZL treated with liso-cel. • The most common adverse events (>20%) were cytokine release syndrome, diarrhea, fatigue, musculoskeletal pain, headache, and tremor.	• The safety profile of lisocabtagene maraleucel is acceptable in the intended population. • The USPI includes a boxed warning for CRS, neurologic toxicities, and T cell malignancies. • The USPI includes warning and precautions for hypersensitivity reactions, serious infections, prolonged cytopenias, hypogammaglobulinemia,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		and secondary malignancies.

1.4. Patient Experience Data

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	
☐	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:

MZL is the third most common lymphoma, accounting for approximately 7% of all B-cell NHLs.[1,2,3] MZL is an indolent mature B cell malignancy and originates from memory B lymphocytes in the marginal zone of the secondary lymphoid follicles within the spleen, lymph nodes, and mucosal lymphoid tissues. Depending on these sites of involvement, MZL is divided into 3 subtypes: EMZL of mucosa-associated lymphoid tissue (gastric and non-gastric MALT lymphoma), NMZL, and SMZL.[2,4,5]

The median age at diagnosis of MZL is 69 years.[2] The incidence increases with age, suggesting cumulative exposure to risk factors. Established risk factors for MZL (or MZL subtypes) include family history of NHL, genetic loci in the human leukocyte antigen region, *Helicobacter pylori* infection (gastric MALT lymphoma), and several autoimmune diseases (Sjögren syndrome, SLE, and Hashimoto thyroiditis), with strong (but not definitive) evidence for *Chlamydia psittaci* (ocular adnexal MALT lymphoma), *Borrelia burgdorferi* (cutaneous MZL), hepatitis C virus, human immunodeficiency virus, and solid organ transplantation.[4]

MZL is characterized by slow growth and often does not require immediate therapy. However, like other indolent lymphomas, some patients have more aggressive disease, associated with worse prognosis. Early progression (occurring in approximately 20% of patients)[6] is associated with particularly poor outcomes, with median overall survival of 3 to 5 years in patients with disease progression within 24 months from initial systemic therapy.[7,8]

The FDA's Assessment:

Marginal zone lymphoma is the third most common type of B cell non-Hodgkin's lymphoma with an incidence of 7460 cases/year in the US. MZL is comprised of three subtypes, extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), splenic MZL, and nodal MZL. Whereas patients with extranodal MZLs often present with symptoms related to tissue involvement of an affected site (e.g. stomach, ocular adnexa, salivary gland, thyroid gland, lung, or skin), patients with splenic MZL and nodal MZL typically present with disseminated disease which may be asymptomatic and not require treatment initially (i.e. lymphocytosis, splenomegaly, or painless lymphadenopathy) until disease progresses and causes cytopenias, massive splenomegaly, or bulky lymphadenopathy. In the absence of symptoms, active surveillance is recommended even in advanced-stage disease with treatment only initiated to alleviate symptoms and improve quality of life. Upfront treatment typically includes rituximab-based therapy whereas single-agent rituximab, rituximab-based chemotherapy regimens, lenalidomide plus rituximab, and zanubrutinib may be administered in the second-line setting and beyond. Median overall survival exceeds 10 years with progression of disease within 2 years after initial treatment being the

strongest prognostic biomarker of reduced survival (i.e. 3-5 years).

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 MZL

Drug Brand Name (Generic Name)/Class	Type of Approval (Date)	Indication	Endpoint(s)[a]	Trial Design (Study)/ Results
RITUXAN® (Rituximab) / CD20-directed cytolytic antibody	Regular Approval (November 1997)	MZL (various subtypes)	ORR, PFS	Multiple studies, including single-arm and combination therapy trials / ORR: varies by study
IMBRUVICA® (ibrutinib)/ BTK Inhibitor	Accelerated Approval (January 2017) Withdrawn (May 2023)	R/R MZL after at least one prior anti-CD20-based therapy	ORR	Single-arm, multicenter trial (PCYC-1121) / ORR: 46%
REVLIMID® (lenalidomide) + RITUXAN (rituximab) / Immunomodulatory agent + CD20-directed cytolytic antibody	Regular Approval (May 2019)	R/R MZL	ORR, PFS	Phase 3, randomized, open-label trial (AUGMENT) / ORR: 80%, PFS: 39.4 months Open label, multicenter trial (MAGNIFY) / ORR: 58.8%
UKONIQ™ (Umbralisib) / PI3K Delta and CK1 Epsilon Inhibitor	Accelerated Approval (February 2021) Withdrawn (May 2022)	R/R MZL	ORR	Single-arm, multicenter trial (UNITY-NHL) / ORR: 49%
BRUKINSA® (zanubrutinib) / BTK Inhibitor	Accelerated Approval (September 2021)	R/R MZL after at least one prior anti-CD20-based therapy	ORR	Single-arm, multicenter trial (BGB-3111-214) / ORR: 56%

[a] Endpoint(s) on which the approval was based.

Unmet Medical Need for Patients with R/R MZL

An SLR[9] 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 3L+ R/R MZL.

The standard of care for R/R MZL has yet to be defined, and depends on various factors, such as disease stage and extent, symptoms, affected organs, previous treatments and their outcomes, comorbidities, and patient preferences.[10,11] Approximately 50% of patients with MZL need systemic therapy. Chemoimmunotherapy regimens that include an anti-CD20 antibody, such as rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP); rituximab, cyclophosphamide, vincristine, prednisone (R-CVP); and bendamustine/rituximab (B-R), are commonly used for treatment of patients with MZL, both in frontline (1L) and in the R/R setting (2L+).[10,11,12,]

Currently, only two regimens are approved for treatment of patients with 2L+ MZL:

rituximab-lenalidomide (R2), which was granted full approval by the FDA in 2019 based on the Phase 3 AUGMENT and MAGNIFY studies[13,14], and the BTK inhibitor, zanubrutinib, which was granted accelerated approval by the FDA in 2021 based on the Phase 2 MAGNOLIA study.[15] Although R2 and zanubrutinib demonstrated promising responses (ORR 65% to 70%; CRR 25% to 40%), there was high rate of AEs, including AEs leading to treatment discontinuation.[15,14,16,17] Additional treatment options such as ibrutinib[18], a BTK inhibitor, and umbralisib[19], a phosphoinositide 3-kinase δ inhibitor, showed promising results in patients with R/R MZL, but they were both withdrawn from the market due to efficacy and safety concerns, respectively. The CAR T-cell therapy axi-cel has demonstrated encouraging efficacy in patients with 3L+ MZL, but the sample size studied is small (n = 31), (b) (4) . Axi-cel is also associated with significant toxicities, including high rates of Grade ≥ 3 CRS, Grade ≥ 3 neurotoxicity, and Grade ≥ 3 infections.[20,21] Due to the lack of standard of care and limited approved therapies, there remains an unmet medical need for new therapies that offer high efficacy with a manageable safety profile for patients with 3L+ MZL, whose disease progresses rapidly and has a poor prognosis.

The FDA's Assessment:

The FDA disagrees with the Sponsor's comment that patients with 3L+ MZL have disease that uniformly progresses rapidly and has a poor prognosis. As mentioned previously, treatment in relapsed or refractory MZL should be individualized based on the presence or absence of histologic transformation, stage and extent of disease, symptoms, organ involvement, number and type of prior treatments, duration of remission, and the patient's performance status. Although patients with MZL may relapse several times, the relapses are generally treatable.

Table 2 provides key outcomes for therapies approved in the US for relapsed or refractory MZL, including two therapies under traditional approval, i.e. bendamustine and the combination of lenalidomide and rituximab, and one therapy under accelerated approval, i.e. zanubrutinib.

Table 2. FDA - Primary Efficacy Results for US Approved Therapies for Treatment of Relapsed or Refractory Marginal Zone Lymphoma

	Zanubrutinib	Lenalidomide plus rituximab	Bendamustine
Approval Type	Accelerated	Traditional	Traditional
Indication	R/R MZL; ≥ 1 anti-CD20 based regimen	Previously treated MZL in combination with rituximab	Indolent B-cell NHL progressed < 6 months of rituximab or rituximab

				containing regimen
Trial	BGB-3111-214	BGB-3111-AU-003	AUGMENT (A) MAGNIFY (M)	NCT00139841
Approval date	9/14/2021		5/28/19	10/31/08
N	66	20	31 (A) 45 (M)	100
ORR (%)	56 (43, 68)	80 (56, 94)	65 (45, 81) (A) 51 (36, 66) (M)	74 (64.3, 82.3)
CR rate (%)	20	20	-	13
Median DOR (months)	2.9 (1.8, 11.1)	NE (8.4, NE)	NR (8, 18.9) (M)	9.2 (7.1, 10.8)

R/R = relapsed or refractory; MZL = marginal zone lymphoma; N= number; ORR = overall response rate; CR complete response; DOR = duration of response
Source: Zanubrutinib USPI, Lenalidomide USPI, and Bendamustine USPI

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
BREYANZI is a CD19-directed genetically modified autologous T-cell immunotherapy that is currently indicated in the US for the treatment of:

- adult patients with LBCL, including DLBCL NOS (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL3B, who have:
  - refractory disease to 1L chemoimmunotherapy or relapse within 12 months of 1L chemoimmunotherapy (sBLA 125714/90; 24-Jun-2022 approval); or
  - refractory disease to 1L chemoimmunotherapy or relapse after 1L chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age
    (BLA 125714/90; 24-Jun-2022 approval); or
  - R/R disease after 2 or more lines of systemic therapy (BLA 125714/0; 05-Feb-2021 approval).

  Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.
- adult patients with R/R CLL or SLL who have received at least 2 prior lines of therapy, including a BTKi and a B-cell lymphoma 2 inhibitor. This indication is approved under

accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) (sBLA 125714/205; 14-Mar-2024 approval).

- adult patients with R/R 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) (sBLA 125714/225; 15-May-2024 approval).
- adult patients with R/R MCL who have received at least 2 prior lines of systemic therapy, including a BTKi (sBLA 125714/227; 30-May-2024 approval).

The FDA's Assessment:

3.2. The review team agrees with the Applicant's summary of US regulatory actions. 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 MZL are summarized in Table 2.

Table 3: Applicant - Key IND Regulatory Activities Relating to Liso-cel MZL Development

Interaction Type / Activity	Purpose	Date	Meeting ID (CRMTS #)
Submission of original protocol JCAR017-FOL-001 to IND 016506 (SN0585)	NA	05-Dec-2019	NA
Type B End of Phase Meeting	To discuss the proposed global Phase 3 confirmatory Study CA082011	13-Jul-2021	13362
Type C Meeting	To review the data from Study JCAR017-FOL-001 and to obtain FDA feedback on: • The planned sample size, follow-up needed for registration in R/R FL and R/R MZL • Primary endpoints and definition from Study JCAR017-FOL- 001 • Key aspects of the format and content of the planned sBLA dossier for R/R FL and R/R MZL	22-Feb-2022	13766
Submission of JCAR017-FOL 001	To incorporate Agency's feedback from 22-Feb-2022 Type C Meeting (CRMTS	15-Aug-2022	NA

Table 3: Applicant - Key IND Regulatory Activities Relating to Liso-cel MZL Development

Interaction Type / Activity	Purpose	Date	Meeting ID (CRMTS #)
protocol amendment 2 to BB-IND 016506 (SN0851)	#13766) such as sample size, extended follow-up, updates to timing of primary analysis in addition to other global updates		
Orphan Designation for NMZL granted	Designation: for treatment of NMZL (DRU-2023-9337)	30-Mar-2023	NA
Orphan Designation for SMZL granted	Designation: for treatment of SMZL (DRU-2023-9336)	17-Apr-2023	NA
Orphan Designation for EMZL granted	Designation: for treatment of EMZL (DRU-2023-9338)	17-Apr-2023	NA
Submission of original Phase 3 protocol CA082011 to BB-IND 016506 (SN0942)	NA	25-Sep-2023	NA
Sponsor Response to Informal Teleconference regarding PMR	To provide alternate proposal for FL and MZL PMR to support the Type B End of Phase meeting planned for 02-Apr-2024	26-Mar-2024	NA
Type B End of Phase Meeting	To discuss the alternate proposals for FL and MZL PMR	02-Apr-2024	20169
Type C Meeting	To obtain FDA feedback on the key aspects of the format and content of the planned sBLA dossier for R/R MZL	15-Oct-2024 (Teleconference canceled at the Sponsor's request. FDA's preliminary comments were received on 10-Oct-2024 and are considered final FDA responses)	20603
Type B pre-sBLA Meeting	To discuss a supplemental BLA submission based on the topline results of Study JCAR017-FOL-001 MZL cohort	04-Apr-2025	21150

The FDA's Assessment:

The FDA highlights the following clarifications made during interactions with the

Applicant as below in Table 4 and notes a communication on 4/9/24 where the FDA indicated that final agreement of the confirmatory trial would occur during the review of the BLA and on 3/22/22 where the FDA indicated that the submission will require data demonstrating advantage of liso-cel over available therapies, which should include an assessment of efficacy in subjects treated previously with R2. During the 3/22/22 communication, the FDA also recommended that all responding subjects have a minimum of 12 months follow-up for DOR, measured from the date of first objective response to the date of last adequate (radiographic) disease assessment.

Table 4: FDA- FDA Summary of Interactions Between the Applicant and the FDA

Meeting ID 21150 4/4/2025	• FDA agreed that submission of clinical efficacy data from 66 patients and clinical safety data from 77 patients with relapsed or refractory MZL treated on Study FOL-001 would support submission of an sBLA for the proposed MZL indication. • FDA noted limited representation of extranodal MZL and splenic MZL in preliminary comments. • FDA asked how investigator identified neurotoxicity was defined and whether it included immune effector cell associated neurotoxicity syndrome in preliminary comments. • FDA agreed to submission of a combined SCS/ISS including safety data from 77 patients with R/R MZL treated on Study FOL-001 and pooled monotherapy safety data from 961 patients with hematologic malignancies. • FDA agreed that no ISE would be submitted. • FDA agreed to the structure and content of the datasets for Study FOL-001. • Applicant clarified that primary analysis of DOR and PFS will be conducted using EMA censoring rules. • Applicant clarified that DOR and PFS using FDA censoring rules will be provided in the BLA submission. • FDA relayed requirement for 90 day safety update given planned priority review • Proposed registry-based post-marketing study was readdressed as described for meeting ID 20603 below. • FDA agreed to submission of updated Pharmacovigilance Plan with sBLA. • FDA referenced March 7, 2025 REMS modification notification letter and indicated that REMS is no longer required for lisocabtagene maraleucel.
Meeting ID 20603 10/10/2024 Preliminary Comments	• FDA indicated that applying Lugano CT-based criteria per IRC for the MZL primary and secondary efficacy assessments based on the Study FOL-001 IRC Charter was acceptable. FDA noted that patients with extranodal disease at screening must undergo biopsy of the extranodal site as part of the disease response assessment. • FDA indicated that the primary analysis should take place when at least 60 patients had been followed for DOR for a minimum of 12

	months after first response as assessed per IRC. • FDA agreed with the Applicant's plan for presentation of efficacy data, safety data, and clinical pharmacology data in the sBLA. The FDA asked for dose levels to be included in the SCS/ISS. • The FDA agreed with the Applicant's plan for submission of safety narratives, efficacy narratives, and CRS for the MZL cohort. The FDA also asked for pathology reports in the sBLA submission when applicable. • The FDA agreed with the structure and content of the datasets for the MZL cohort. • The FDA agreed with the proposed Table of Contents for the sBLA submission. • FDA indicated that the Applicant's plan for a postmarketing study collecting data on patients with relapsed or refractory MZL treated with liso-cel with endpoints of secondary malignancies and long-term safety in the real-world setting was acceptable. The FDA indicated that review decisions would be made once the concept protocol was submitted with the future sBLA.
Meeting ID 20169 4/9/2024	• Discussed confirmatory study, substudy 3 of Study CA082011, i.e. a randomized controlled trial of liso-cel vs standard of care in 60 patients with 3L+ R/R MZL, to confirm the clinical benefit of liso-cel. • FDA noted that plan proposed during informal teleconference 3/22/2024… "appears to be acceptable". • FDA preliminary comments noted that "final agreement of the confirmatory trial occurs during the review of the BLA." • During the meeting, the Applicant proposed a sample size of 67 patients treated with liso-cel on a single-arm trial with at least 24 months of response follow-up to confirm clinical benefit in patients with relapsed or refractory MZL. "The Agency stated that it is premature to agree with the proposed approach." • The FDA noted that the proposed inclusion and exclusion criteria, comparators for investigator's choice of SOC options, and the main estimand for the primary objective of the 3L+ MZL Sub-study 3 under study CA082011 appeared acceptable.
Informal_Teleconference 3/22/2024	• Applicant discussed using additional follow up for responders treated on Cohort 4 of FOL-011 Study_CA082011, i.e. at least 24 months from the first objective response for all responders, to verify clinical benefit of liso-cel for the treatment of 3L+ R/R MZL.
Type C 3/22/22	• FDA agreed that patients with relapsed or refractory MZL after two or more lines of therapy have high unmet medical need. • FDA agreed that IRC assessed ORR applying Lugano criteria among subjects with FL or MZL who received liso-cel is an acceptable primary endpoint, with CT based criteria alone used in MZL. • The Applicant agreed that bone marrow biopsy would be conducted at screening for MZL patients with a requirement to repeat the bone marrow biopsy to confirm a CR on CT among subjects with a positive, indeterminate, or unknown bone marrow biopsy at baseline. Otherwise the CR would be downgraded to a PR.

	• FDA advised the Applicant to increase the number of MZL subjects above 40 and to ensure there would be an adequate representation of various MZL subtypes in the study population. • FDA stated that the adequacy of the data to support registration would take into consideration the populations studied, the limitations of a single-arm study design, the durability of the treatment effect, and the adequacy of duration of response followup, the overall benefit-risk profile of the investigational therapy in the context of available therapies, which includes lenalidomide and rituximab (R2). • FDA indicated that the submission will require data demonstrating advantage of liso-cel over available therapies, which should include an assessment of efficacy in subjects treated previously with R2. • FDA advised that all responding subjects have a minimum of 12 months followup for DOR, measured from the date of first objective response to the date of last adequate (radiographic) disease assessment. • The FDA clarified that the main analysis of DOR should utilize FDA censoring rules.

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

Product Quality
There are no outstanding issues with product quality.

4.2. 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:
Results from pharmacokinetics, pharmacodynamics, and immunogenicity evaluated in the 3L+ R/R MZL Cohort 4 of Study JCAR017-FOL-001 (hereafter referred to as 3L+ MZL subjects and Study FOL-001, respectively) are highlighted in this section.

Pharmacokinetics
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. The median Cmax, AUC(0-28) and Tmax were 81390 copies/µg, 657799 day*copies/µg, and 10.0 days, respectively. Persistence of the liso-cel transgene was observed up to Month 42 (Day 1275).

No relevant differences in transgene PK parameters by subgroups were observed, except for a potential association between sex and AUC(0-28), with males showing higher AUC(0-28) compared to females. However, there was large intersubject variability (geometric CV% > 150) in AUC(0-28) for both sexes, with overlapping ranges of AUC(0-28) between the two groups.

Pharmacodynamics
B-cell aplasia was observed in 71.2% of subjects at baseline and increased to 90.8% of subjects by Day 8. B-cell aplasia was maintained in over 90.3% of subjects through Day 90 and continued to be observed in 68.4% of subjects who reached Day 730 (24 months).

IgG level < 500 mg/dL was observed in 40.7% of subjects at baseline, increased to 60.7% of subjects on Day 60, and then decreased to 52.5% by Day 730 (24 months). The analysis of serum IgG levels did not take into account potential confounding by the administration of IVIG for the treatment of hypogammaglobulinemia.

Median IgG levels were lower than baseline from Day 15 to Day 1095 (36 months).

Plasma cytokine, such as IL-2, generally peaked on Day 4 and returned to median baseline or below baseline levels by Day 29 post liso-cel infusion.

Pharmacokinetic-Efficacy/Safety Relationships
A potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and longer DOR if BOR is CR per IRC. No apparent relationship was observed between transgene PK parameters and CR, PFS, and DOR per IRC. The number of non-responders was too low to assess any potential relationship with response.

A potential relationship was observed between higher transgene PK parameters (Cmax, AUC[0-28]) and a higher incidence of any-grade CRS and any-grade iiNT. The frequency of Grade ≥ 3 CRS (n = 3) and iiNT (n = 3) was too low to assess any potential relationship with these events.

Pharmacodynamic-Safety Relationships
No baseline levels of any soluble biomarker, CRP, or ferritin were associated with CRS

or iiNT. Peak levels of amyloid A and IL-6 were associated with any-grade CRS, while peak CRP levels were associated with any-grade iiNT. The frequency of Grade ≥ 3 CRS (n = 3) and iiNT (n = 3) was too low to assess any potential relationship with these events.

Immunogenicity

The prevalence of ATA was 0% (0 of 66 subjects); the incidence of ATA was 19.7% (13 of 66 subjects). Meaningful conclusions could not be drawn regarding the relationship between ATA incidence and efficacy, safety or PK due to the limited number of subjects in subgroups within those with treatment-induced ATA, as well as large variability in PK parameters.

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

The Phase 1 trial, Study 017001, evaluated liso-cel in aggressive large B-cell NHL at several DLs and infusion schedules after LDC with cyclophosphamide (300 mg/m^2/day x 3 days) and fludarabine (30 mg/m^2/day x 3 days). Safety and efficacy of 102 subjects treated at either DL1 (50 × 10^6 CAR+ T Cells) or DL2 (100 × 10^6 CAR+ T Cells) showed good tolerability and efficacy with a single liso-cel infusion.[22,23] DL2 was selected as the recommended dose for the dose-confirmation cohort in DLBCL and therefore was selected for the Study FOL-001.

Although the planned dose was 100 × 10^6 CAR+ T cells, a dose range of 90 to 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 based on available data supporting efficacy at doses lower than 100 × 10^6 and safety with doses up to 110 × 10^6.

Clinical efficacy and safety results: In Study FOL-001 MZL Cohort 4, liso-cel dose of 100 × 10^6 CAR+ T cells demonstrated clinically meaningful efficacy in 3L+ MZL subjects with high ORR, CRR, and durable responses (Table 13 and Table 14). The median number of total (CD8+ and CD4+) liso-cel dose administered for 3L+ MZL was 100.15 × 10^6 CAR+ T cells (range: 97.3 × 10^6 to 102.8 × 10^6), which was within the proposed liso-cel dose range of 90 to 110 × 10^6 CAR+ T cells.

The overall safety profile of liso-cel in 3L+ MZL was manageable and consistent with that previously observed in the marketed indications of R/R 2L/3L+ LBCL, 3L+ CLL/SLL, 3L+ FL, and 3L+ MCL, with no new safety concerns.

PK/Pharmacodynamic results: Results from the PK/pharmacodynamic analyses in 3L+ MZL demonstrated that the established benefit-risk profile in MZL remains unaffected by liso-cel exposure at the proposed dose range of 90 to 110 × 10^6 CAR+ T cells.

The FDA's Assessment:

FDA concur with the Applicant's assessment.

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	Indication
JCAR017-FOL-001 (TRANSCEND FL) Regions: US, Europe, Japan, Canada	Phase 2, Open-label, single-arm, multicohort, liso-cel monotherapy	Adult 2L+ iNHL (3L+ MZL from Cohort 4)	100 × 10^6	Ongoing 29-Nov-2024 67 (Cohort 4 MZL)	3L+ MZL
GC-LTFU-001 Regions: US, Europe, Japan	Interventional multi-site	All subjects treated with a Applicant CAR+ T-cell therapy, including liso-cel	NA	Ongoing 31-Jan-2024 0 (Cohort 4 MZL)[a]	

[a] As of the data cutoff date, Study GC-LTFU-001 had not enrolled any subject from the MZL Cohort of Study FOL-001; the following monotherapy liso-cel-treated subjects were enrolled and safety data from LTFU were integrated with parent studies for pooled safety analyses: 19 from 017004 Monotherapy, 1 from FOL-001, 16 from 017001 MCL Cohort, 22 from BCM-001, and 25 from 017007.

The FDA's Assessment:

FDA agrees with the Applicant's description of JCAR017-FOL-01. Cohort 4 of Study FOL-001 is the primary study in support of this Biologics License Application (BLA). However, GC-LTFU-001 is a non-interventional study, not an interventional one.

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 (MZL Cohort: JCAR017-FOL-001; NCT04245839) 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 4).
Results provided in this document cover only subjects with 3L+ MZL. Results for subjects with 3L+ FL (Cohorts 1 and 2) were provided in a separate sBLA application (sBLA

125714/225) based on which the FDA granted accelerated approval of liso-cel in 3L+ FL (15-May-2024).

Figure 1: Applicant - Study FOL-001 Study Design

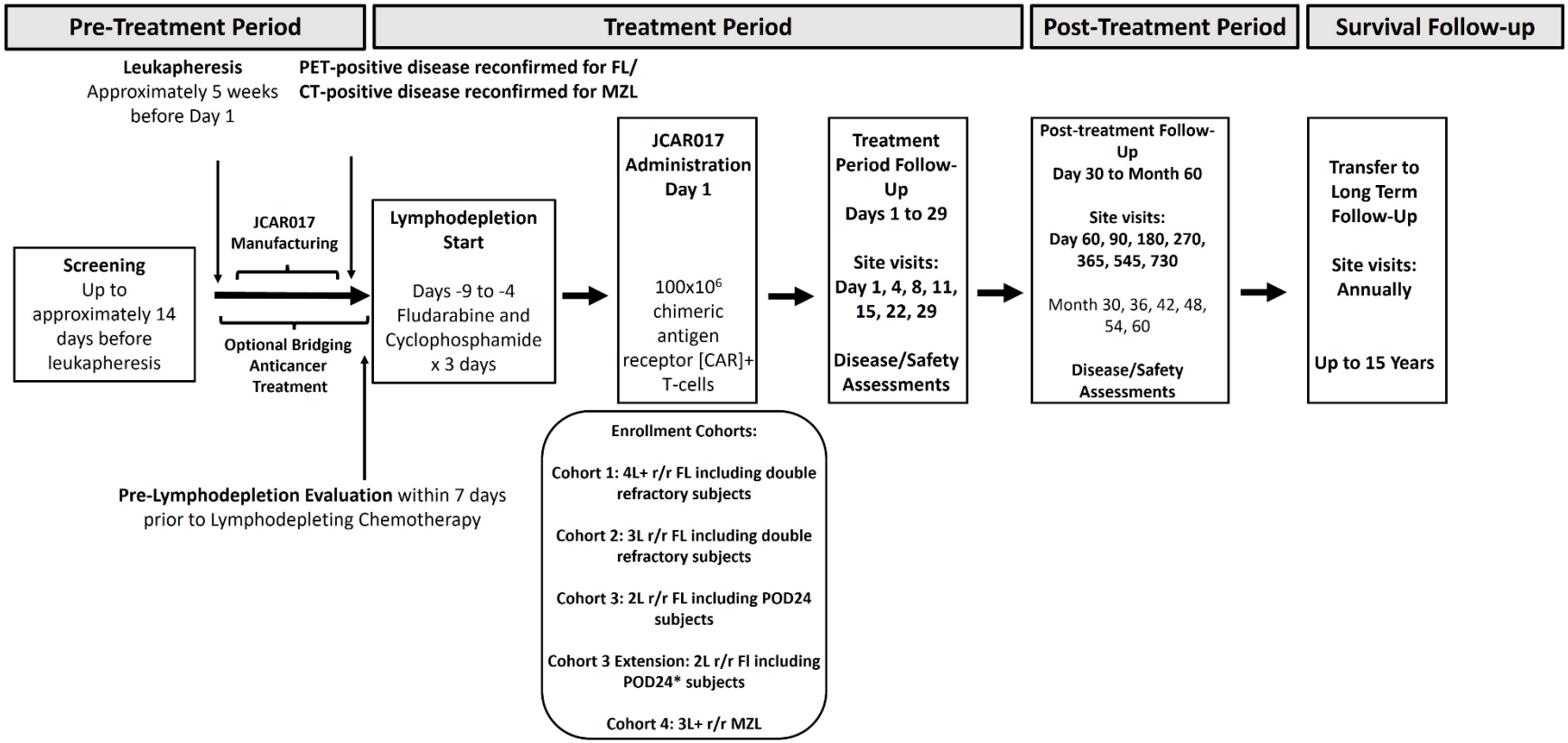


Table 6: Applicant - Study FOL-001 Study Design

Study Design	The study is divided into 3 periods: Pretreatment (screening assessments, leukapheresis, and pretreatment evaluation), Treatment (starting with the administration of LDC and continuing 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, subjects were asked to consent to participate in a Long-term Follow-up study for up to 15 years after the dose of liso-cel. Approximately 276 subjects were expected to be enrolled worldwide with the aim to treat approximately 227 subjects across 5 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 3 Extension (2L R/R FL): approximately 57 treated subjects. Cohort 4 (3L+ R/R MZL): approximately 60 treated subjects. Following confirmation of study eligibility, all subjects underwent 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 subjects must meet eligibility criteria after completion of that treatment. The pretreatment PET (required for FL subjects and MZL subjects with FDG-avid disease) 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. 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 and continue until Day 29 after infusion
Study Population	For Cohort 4 of Study FOL-001, adult subjects with MZL histologically confirmed per local pathologist assessment and R/R disease as assessed by the investigator. Subjects must have had measurable disease and received at least 2 prior systemic therapies, including at least one line of systemic therapy with anti-CD20 antibody and alkylating agent, or relapsed after HSCT. Splenectomy for SMZL was considered as a line of therapy. Antibiotics for EMZL were not considered as a prior line of therapy. Subjects had an ECOG performance status of 0 or 1, and adequate organ functions.
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	For 3L+ MZL subjects, the efficacy was assessed by radiographic tumor evaluation by diagnostic quality CT/MRI scans according to the Lugano classification[24], assessed by an IRC. A negative BMB was required to confirm initial CR by CT/MRI in subjects that had bone marrow involvement by lymphoma at screening. Subjects with gastric mucosa-associated lymphoid tissue lymphoma also underwent upper gastrointestinal endoscopy/biopsy to confirm CR by CT/MRI. Upon documentation of PD or administration of additional anticancer treatment, response assessments were no longer required. Disease assessments were performed at screening, prior to LDC (for subjects who received bridging therapy), on Day 29 after liso-cel infusion, and during follow-up period (Days 90, 180, 270, 365, 545, 730 [Month 24], and Months 36, 48, and 60 [end of study] after liso-cel administration).

Table 6: Applicant - Study FOL-001 Study Design

Safety Assessments	Safety evaluations included AE/SAE collection, concomitant medication and procedure assessment, laboratory evaluations, physical examinations, and vital sign assessment. AEs and laboratory abnormalities (type, frequency, and severity) were collected, graded, and reported according to CTCAE (version 5.0). CRS was graded by the Lee criteria (2014).[25]. All AEs were coded using the MedDRA dictionary (version 26.0). The study data were regularly reviewed by an independent data safety monitoring board. All AEs from the start of LDC until Day 90 after liso-cel infusion (defined as TEAEs) must have been reported and only AEs that were considered related to study procedures needed to be reported beyond Day 90.
Study Status	First subject first visit for MZL: 11-Nov-2020. Study is ongoing.

The study was conducted at 29 sites in 10 countries (Austria, Canada, France, Germany, Italy, Japan, Spain, Sweden, UK and US) for MZL treated subjects. 32 out of the 67 (47.8%) MZL subjects treated with liso-cel were enrolled at US sites. Review of the baseline demographics and clinical characteristics of the enrolled MZL subjects (Table 10) and comparison to the overall R/R MZL population in the US suggested that the study subjects adequately represented the overall US 3L+ MZL population, including all three subtypes.

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

The FDA's Assessment:

The FDA agrees with the Applicant's description of Study FOL-001 as applicable to the MZL Cohort (i.e. Cohort 4). The FDA clarifies however, that the ITT population enrolled at 30 sites, not 29, as extracted from the ADSL dataset. 38 (49%) patients were enrolled from the US, 11 (14%) from France, 6 (7.8%) from Italy, 5 (6.5%) each from Germany and Spain, 4 (5.2%) from Great Britain, 3 (3.9%) from Sweden, and 2 (2.6%) each from Canada and Japan and 1 from Austria (1.3%). The FDA's efficacy analyses included assessment of efficacy in the leukapheresed population (n=77) and in treated patients (n=66) who had measurable disease on CT scan at baseline, received treatment with conforming at intended dose range, and had at least 9 months of follow up for duration of response since the onset of first response. The treated population includes only 17 patients with extranodal MZL and 18 patients with splenic MZL, which provides limited representation of subjects with extranodal and splenic MZL. The FDA further notes inclusion criteria for the MZL cohort otherwise included the presence of measurable disease defined as a nodal lesion greater than 2.0 cm in the long axis at baseline or at least one measurable extranodal lesion if no measurable nodal lesion greater than 2 cm was present. The FDA notes that measurable nodal disease per Lugano 2014 criteria requires the longest diameter be greater than 1.5 cm. A measurable extranodal lesion per Lugano 2014 criteria requires the longest diameter be greater than 1.0 cm.

Relapsed or refractory MZL patients enrolling on Cohort 4 of Study FOL-001 were not

required to have an indication for systemic treatment for study enrollment (i.e. symptoms of threatened end-organ function, clinically significant or progressive cytopenias, clinically significant bulky disease, or rapidly progressive disease). Patients were assessed to have relapsed or refractory disease per the investigator's clinical assessment. In response to an FDA Information Request submitted by the Applicant on August 8, 2025, the Applicant clarified that meeting one or more GELF criteria was not required for the MZL Cohort eligibility, and these criteria were not systematically collected for the MZL Cohort on Study FOL-001. In a follow up Information Request dated August 20, 2025, the FDA inquired about 20 MZL patients who did not meet criteria for treatment based on B symptoms, cytopenias, bulky disease, splenomegaly, and POD24 disease as captured in the datasets. The Applicant responded on August 25, 2025 with additional information on disease characteristics for the 20 subjects and clinical rationale for treatment as provided by investigators as a follow up to the Applicant's query in response to the FDA IR. The FDA concurs with the indication for treatment as provided by the investigators for 16 out of 20 patients. The FDA, however, notes the administration of liso-cel in 2 subjects with early stage MZL, i.e. one stage 1 patient with a prior history of CNS involvement which is a highly unusual presentation for MZL and one stage 2 patient who was s/p autologous stem cell transplant treatment which is also a highly unusual treatment for MZL in early lines of therapy. A third patient was treated in the fourth line setting for symptoms of pain which is not a typical reason for initiation of treatment in MZL although the patient demonstrated lack of response to prior lines of therapy. Finally, a 46 y/o subject with stage 3 disease who had received at least 2 lines of systemic therapy received liso-cel for relapsed disease within 6 months of single agent Rituxan given the presence of paravertebral lesions and potential risk of neurologic compromise, again an unusual presentation for MZL.

Table 77: FDA- Summary of Reasons for Administration of Liso-cel per Investigator

USUBJID	Patient history
(b) (6)	60 y/o subject with stage 1 MZL, s/p 2 lines of systemic treatment and refractory to rituximab, bendamustine, and ibrutinib in last line of treatment, with 1 nodal target lesion and 1 nodal non-target lesion at screening. Investigator noted prior history of CNS involvement.
(b) (6)	63 y/o subject with stage 4 MZL, s/p 3 lines of systemic therapy, refractory to rituximab and lenalidomide with last line of treatment, with 3 nodal target lesions and bone marrow involvement at screening, treated for symptoms of pain and lack of response to prior lines of therapy.

(b) (6)	54 y/o subject with stage 2 MZL, s/p 2 lines of systemic therapy, including ASCT, with relapsed disease 9 months after gemcitabine, ifosfamide, oxaliplatin, and rituximab, with 1 extranodal lesion in the kidney measuring 5 cm.
(b) (6)	46 y/o subject with stage 3 MZL, s/p 2 lines of systemic therapy, relapsed 6 months after receiving single agent rituximab, with 3 target lesions and 5 non-target lesions at screening, treated for the presence of paravertebral lesions that posed a risk of neurologic complications for the subject.
Source: Applicant's response to FDA information request dated 8/25/25	

Finally, the SAP version 4 (dated May 14, 2024) notes that a subset of subjects with high-risk features, including double refractory and subjects with progression of disease within 24 months (POD24) will be included in the efficacy population. Double refractory as defined by the Applicant includes subjects with no response or progression during or up to 6 months after completing treatment with rituximab and an alkylating agent. POD24 subjects are defined as subjects that have progressed or relapsed within 24 months of diagnosis. The FDA clarifies that POD24 refers to subjects with progression of disease (POD) within 2 years of diagnosis in subjects treated with front-line chemoimmunotherapy (Casulo 2015).

Study Endpoints

The Applicant's Description:

Table 88: Applicant - Study FOL-001 Endpoints as Applicable to Cohort 4 3L+ MZL

Endpoint	Endpoint Description
Primary Endpoint	
ORR as assessed by CT using the Lugano classification.[24]	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 CT using the Lugano classification.	Percentage of subjects achieving a CR at any time up to 60 months after liso-cel treatment (EOS).
DOR as assessed by CT using the Lugano classification.	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 CT using the Lugano classification.	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).
PFS as assessed by CT using the Lugano classification.	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).

Table 88: Applicant - Study FOL-001 Endpoints as Applicable to Cohort 4 3L+ MZL

Endpoint	Endpoint Description
OS	Time from start of liso-cel to death from 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[a]	• 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).
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).

For assessment of the response and progression endpoints, bone marrow biopsy was used to evaluate bone marrow lymphoma involvement.
[a] 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 of efficacy was based on the primary endpoint of ORR defined as the percentage of subjects with a best overall response of complete response (CR) or partial response (PR), as confirmed by IRC per Lugano classification (Cheson 2014) and further supported by duration of response (DOR). The efficacy analyses were performed both in the intention-to-treat (all leukapheresed) population as well as in the

treated efficacy population. Time to event endpoints, including PFS and OS, from a single arm trial are not interpretable and considered exploratory. FDA censoring rules were applied for the analysis of DOR and PFS.

The original protocol version 1, dated November 11, 2019 indicated that efficacy would be evaluated based on "Celgene interpretation of the Lugano Classification". In response to an FDA Information Request on August 25, 2025, the Applicant clarified that the "Modified Lugano Classification Criteria" applied only to response assessments by PET and were only applicable to the FL Cohorts of Study FOL-001 where PET was used for radiographic assessment. The Applicant confirmed that radiographic assessment for the MZL subjects was performed using CT-scans and had no discrepancies with the CT-based response criteria as per the 2014 Lugano Criteria.

The IRC charter notes that the CT portion of a PET/CT can be submitted in lieu of a dedicated CT. As communicated by the Applicant on September 29, 2025 in a response to an FDA Information request, CTs obtained on hybrid PET/CT systems meet diagnostic quality standards even without contrast, are not considered low-dose attenuation correction scans, and offer optimal spatial resolution (as per the IRC vendor).

In preliminary meeting responses (CRMTS # 20603), the FDA indicated agreement with the Applicant's intent to apply Lugano CT-based criteria per IRC for the MZL primary and secondary efficacy assessments.

The FDA notes the timeframe of 60 months used by the Applicant to capture all primary and secondary endpoints except HRQoL parameters which were assessed up to 24 months after liso-cel treatment.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Sample size: Assuming a 20% drop out rate, approximately 75 subjects were to be enrolled to ensure that approximately 60 subjects in Cohort 4 would be treated with liso-cel. With a sample size of around 60 treated subjects and using one-sided 0.025 level testing, there would be 90% power to detect an ORR greater than 50% or a CRR greater than 5%.

Efficacy analyses were performed on the Liso-cel-treated Efficacy Analysis Set of Cohort 4 (3L+ MZL). Selected efficacy analyses (ORR, CRR, DOR, PFS and OS) were also performed based on the Leukapheresed (ITT) Analysis Set.

Primary endpoint was ORR, assessed by CT (MZL) using the Lugano classification by an IRC.[24] The primary efficacy analyses were based on the Liso-cel-treated Efficacy Analysis Set.

The primary analysis for Cohort 4 was performed when approximately 60 subjects had been 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.

Key secondary endpoints of CRR, DOR, and PFS per IRC were all assessed by CT (MZL) using the Lugano classification.[24] DOR, DOR for subjects whose BOR was CR, 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 primary analyses were conducted using EMA censoring rules. The OS analysis was planned to include all available survival information including long-term follow-up data.

Sensitivity analyses of primary and secondary efficacy endpoints were performed:

- Per the response assessed by the Investigator.
- In the Leukapheresed (ITT) Analysis Set. A subject in the Leukapheresed (ITT) Analysis 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) Analysis 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.

Sensitivity analyses were performed using FDA censoring rules for DOR and PFS.

Subgroup analyses were performed based on demographic variables from the subject's baseline status, such as age, sex, ethnicity, race, MZL subtype, high risk characteristics (eg, POD24 status), prior anticancer treatments and anticancer treatment for disease control (bridging therapy), concomitant GCSF use. Subgroup analyses were performed for 3L+ MZL subjects for the primary and secondary efficacy endpoints: ORR, CRR, DOR, PFS, and OS. Subgroup analyses were only performed if there were at least 5 subjects in each subgroup.

HRQoL: Key analyses included data completion and compliance rates, as well as group descriptive analyses and mean changes from baseline (within-group clinically meaningful change thresholds were prespecified in the SAP).

The FDA's Assessment:

FDA's efficacy analyses were performed on 1) all leukapheresed population (n=77), and 2) treated population (n=66) who had: relapsed or refractory MZL after 2 or more prior lines of therapy, measurable disease at baseline as per Lugano 2014 criteria (Cheson 2014), received treatment with conforming liso-cel at the intended dose (90 to 110 X 10^6 CAR positive T cells), and had a minimum of 9 months follow up for DOR as assessed per IRC.

Protocol Amendments

The Applicant's Description:

Key study level changes to Study FOL-001 after the original protocol (dated 11-Nov-2019), as applicable to 3L+ MZL subjects are provided below and in Table 6.

In Protocol Amendment 1.0 (06-Jul-2021), the primary endpoint was changed from CRR to ORR and secondary endpoint from ORR to CRR, 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.

In Protocol Amendment 2.0 (10-Jul-2022), the total number of subjects in the study was increased, with 20 additional subjects in the MZL Cohort.

In Protocol Amendment 3.0 (10-May-2024), the assessment window for the Day 730 visit was modified from ± 30 days to 0/+90 days for subjects in the MZL Cohort.

Table 9 9: Applicant - Summary of Key Changes to Study FOL-001 Protocol as Applicable to Cohort 4 3L+ MZL

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 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, with 20 additional subjects in the MZL Cohort	213	181
Protocol Amendment 3.0 / 10-May 2024	• Modified the assessment window for the Day 730 visit from ± 30 days to 0/+90 days for subjects in Cohort 4 (R/R MZL) to enable disease assessment at 24 months after the first objective disease response for responders	276	201

The FDA's Assessment:

The FDA notes the following additional clarifications provided with Amendment No. 1 and Amendment No. 2 and provides the content of Amendment No. 4.

Table 1010: FDA - Summary of Key Changes to Study FOL-001 Protocol as Applicable to Cohort 4 3L+ MZL

Protocol Amendment	Key Revisions
Amendment No. 1 July 6, 2021	• Revised definition of POD24 as those that have progressed within 24 months of diagnosis after treatment with an anti-CD20 antibody and an alkylating agent within the first 6 months of initial FL diagnosis. • Revised definition of double refractory to subjects who are refractory to both an anti-CD20 antibody and an alkylating agent (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 those who are refractory to anti-CD20 maintenance therapy (subjects who did not respond or progressed during or up to 6 months after completing maintenance treatment with an anti-CD20 monoclonal antibody) • Clarified that subjects that received allo HSCT within 90 days of leukapheresis are excluded from the study • Clarified that bone marrow biopsy would be required in the MZL cohort to confirm an initial CR by CT in subjects that had bone marrow involvement by lymphoma at screening • Added that replication competent lentivirus testing should be conducted upon progression • Added that peripheral blood Anti-SARS-CoV-2 serology would be required on days 180, 365, 545, and 730 or at the end of study visit in addition to 4 weeks after a known/suspected COVID-19 infection • Indicated plan to use of CTCAE version 5 to assess organ toxicity for CRS
Amendment No 2 July 10 2022	• Clarified timing of primary analysis to occur when 60 R/R MZL subjects have been followed for duration of response 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 • Window for assessments for day 365 visit window was increased from +/- 30 days to

	-30/+90 days and day +545 visit was increased from +/- 30 days to -90/+30 days • Clarified that PET scan is only required for MZL subjects with FDG avid disease • Increased enrollment period from 18 to 30 months
Amendment No 4 October 11 2024	• Incorporated DSMB for Cohort 3 Extension (2L relapsed or refractory FL).

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 sites closed due to GCP-related issues, and no serious breaches were reported. There were 3 GCP deviations which included: a delay in safety notification to investigators, missing chain of identity information on apheresis documents, and late receipt of regulatory approval dates from CRO. None of the deviations significantly impacted the study.

The FDA's Assessment:
FDA agrees with the Applicant's description.

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 Study 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 17.2

Patient Disposition

Data:

Table 11 11: Applicant - Analysis Populations - Screened Set

Analysis Population, n (%)	3L+ MZL (Cohort 4) n (%)
Screened Set: Subjects who signed informed consent.	84
Eligible Set: Subjects who signed informed consent who meet all inclusion/exclusion criteria.	77
Leukapheresed (ITT) Analysis Set: Subjects who signed informed consent, meet all inclusion/exclusion criteria, and undergo leukapheresis.	77 (100.0)
Liso-cel-treated Analysis Set: Subjects who have received a dose of conforming liso-cel.	67 (87.0)
Liso-cel-treated Efficacy Analysis Set Subjects in the Liso-cel treated Analysis Set who have positive disease present before liso-cel administration based on IRC assessment (CT for MZL). Subjects without baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration were excluded.[a]	66 (85.7)
Outpatient Analysis Set: Subjects in the Liso-cel treated Analysis Set who are monitored as an outpatient.	13 (16.9)
PK Analysis Set: Subjects in the Liso-cel treated Analysis Set who have any available PK measurements by PCR.	67 (87.0)
PK Evaluable Analysis Set: A subset of subjects in the PK Analysis Set who have at least one evaluable PK parameter.	66 (85.7)
PRO Analysis Set: Subjects in the Liso-cel treated Analysis Set who completed pre-LDC PRO questionnaires and have at least one post baseline PRO measurement	61 (79.2)

[a] One subject was excluded from the Efficacy Set due to lack of baseline assessment repeated after anticancer therapy for disease control and before liso-cel administration.
Percentages are based on Leukapheresed (ITT) Set.
Source: ADSL, ADCORE

Table 12 12: Applicant - Key Dates and Follow-up - Study FOL-001

First Subject First Visit	14-Jul-2020 (Study FOL-001) 11-Nov-2020 (3L+ MZL Cohort 4)
First MZL Subject Enrolled (Day of Leukapheresis)	19-Nov-2020
Last MZL Subject Enrolled (and Treated)	07-Sep-2023 (31-Oct-2023)
MZL Clinical Data Cutoff	29-Nov-2024
MZL Database Lock	20-Jan-2025
Median on-study follow-up, months (range: min, max)	24.08 (1.1, 43.0)

Source: ADSL, ADCORE

Table 13 13: Applicant - Subject Disposition - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67) n (%)
Subjects Received Liso-cel	67 (100.0)
Subjects Ongoing on Treatment Period	0
Subjects Completed Treatment Period	66 (98.5)
Subjects Discontinued Treatment Period	1 (1.5)
Primary Reason for Treatment Period Discontinuation	

Table 13 13: Applicant - Subject Disposition - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67) n (%)
Death	1 (1.5)
Subjects Continued to Posttreatment Follow-Up Period	66 (98.5)
Subjects Ongoing on Posttreatment Follow-Up Period	57 (85.1)
Subjects Completed Posttreatment Follow-Up Period	0
Subjects Discontinued Posttreatment Follow-Up Period	9 (13.4)
Primary Reason for Discontinuing Posttreatment Follow-Up Period	
Death[a]	8 (11.9)
Withdrawal by Subject	1 (1.5)
Subjects Discontinued Posttreatment Follow-Up Period Due to COVID-19	1 (1.5)
Subjects Continued to LTFU Protocol	
Yes	0
No	10 (14.9)
Reason Subject Did Not Continue to LTFU Protocol	
Death	8 (11.9)
Progressive Disease	1 (1.5)
Subject Refused	1 (1.5)

[a] Includes one subject death due to COVID-19.

Treatment Period was defined as the initiation of LDC and concluded 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.

Source: ADSL, ADCORE

The Applicant's Position:

The Liso-cel-treated Efficacy Analysis Set (N = 66) was the primary population used for the efficacy analyses and the Liso-cel-treated Analysis Set (N = 67) was the primary population used for the safety analyses (Table 7).

As of the clinical data cutoff date (Table 8), Cohort 4 had completed enrollment. Of the 84 subjects screened, 77 (91.7%) subjects were leukapheresed. Of the 77 leukapheresed subjects, 69 (89.6%) subjects entered the treatment period; 67 (87.0%) subjects were infused with liso-cel and 2 (2.6%) subjects were treated with nonconforming product. 66 of 67 (98.5%) liso-cel infused subjects completed the treatment period (Day 1 to Day 29 after liso-cel infusion) and continued to posttreatment follow-up period (Day 30 to Month 60); 57 (85.1%) subjects were ongoing in the posttreatment follow-up period at the data cutoff date (Table 9).

The FDA's Assessment:

A total of 84 patients with MZL were screened for Study FOL-001; 77 underwent leukapheresis. Prior to administration of lymphodepleting chemotherapy and liso-cel, subjects were not permitted to experience a significant worsening in their clinical status compared to the initial eligibility criteria. Active infections had to resolve and organ toxicities had to recover to < grade 2 prior to administration of liso-cel. Sixty seven subjects were treated with conforming product. 2 subjects received nonconforming

product. All 67 subjects had received 2 or more prior lines of therapy with 66 patients used for the primary analysis of efficacy in the treated population.

There are a total of 10 patients who discontinued therapy and did not receive conforming liso-cel product for the following reasons: administration of nonconforming product in two patients, progressive disease in four patients, failure to meet treatment criteria in three patients including one with cardiovascular complications, and suicide as shown in the table below.

There are a total of 10 patients who discontinued treatment with conforming liso-cel product for the following reasons: T cell lymphoma, neutropenic sepsis with concurrent neurologic toxicities, AML, pneumonia in setting of treatment for MDS, pneumonia in setting of JAK inhibitor prescribed for new onset systemic autoimmune disease, sudden cardiac death, SARS-COV-2, respiratory failure following new anti-lymphoma therapy, sepsis during new antilymphoma therapy, and withdrawal of consent in a patient who received nonconforming product.

Table 14 14: FDA - Subject Disposition -Reasons for Discontinuation from Study FOL-001

Patient ID	Reason for discontinuation of therapy	Clinical history
(b) (6)	Withdrawal	Nonconforming product. 77 y/o woman with stage IV splenic marginal zone lymphoma. Course was notable for day 1 grade 2 insomnia, day 2 grade 3 hypoxia in setting of bilateral malignant pleural effusions that ultimately required pleurodesis (right on day 45; left on day 71), day 4 grade 3 CRS requiring tocilizumab (day 4) and anakinra (day 5), and day 4 grade 1 investigator-identified neurotoxicity requiring decadron between days 4-9. Subject experienced a day 73 grade 3 bacterial pneumonia which resolved on day 77 with episode of delirium on the same day that resolved on day 81. Subject withdrew consent on day 607.
(b) (6)	Death	71 y/o man with stage 4 nodal MZL who died due to progressive disease. No autopsy.
(b) (6)	Death	81 y/o man with stage 4 splenic MZL who received bridging therapy (b) (6) and died (b) (6) due to progressive disease. No autopsy.
(b) (6)	Death	Failure to meet treatment criteria
(b) (6)	Death	68 y/o man with stage 4 extranodal MALT died during pretreatment period due to progressive disease. No autopsy.
(b) (6)	Death	Nonconforming product. 67 y/o man with stage 4 nodal MZL. Vaccinated against COVID19 (b) (6) with booster dose of

		COVID-19 on day 272 ((b) (6)). COVID-19 death on day 358.
(b) (6)	Death	65 y/o woman with stage IV nodal MZL with progressive disease.
(b) (6)	Death	Suicide
(b) (6)	Death	Failure to meet treatment criteria plus cardiovascular complications
(b) (6)	Death	Failure to meet treatment criteria

Table 15 summarizes the reasons for discontinuation from treatment in patients treated with conforming liso-cel product in safety population

Table 1515: FDA - Summary of Reasons for Discontinuation from Treatment in Patients Treated with Conforming Liso-Cel Product in Safety Population- Study FOL-001

Patient ID	Reason for discontinuation of therapy	Clinical history
(b) (6)	Withdrawal	Day 710 withdrawal of consent. 73 y/o woman with stage 2 extranodal MALT MZL. Course complicated by grade 1 CRS on day 6, investigator-identified neurotoxicity on day 8 requiring decadron through day 9. Neurotoxicity resolved on day 10.
	Death	Day 775 pneumonia following treatment for grade 4 MDS diagnosed day 552.
	Death	Day 396 respiratory failure following new anti-lymphoma therapy on day 238.
	Death	Day 803 sudden cardiac death.
	Death	Day 1058 Klebsiella pneumonia death while on JAK inhibitor in setting of systemic granulomatous process that started 177.
	Death	Day 32 T cell lymphoma death.
	Death	Day 490 death due to AML diagnosed on day 430.
	Death	D346 SARS-COV2 infection death.
	Death	Day 416 sepsis during new antilymphoma therapy.
	Death	Day 47 neutropenic sepsis with multiple unresolved concurrent neurologic toxicities at the time of death.

Protocol Violations/Deviations

The Applicant's Position:
IPDs 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 (29-Nov-2024), there was 1 (1.3%) IPD related to procedures/tests.

Two (2.6%) COVID-19 related protocol deviations related to visit schedule were reported.

None of these protocol deviations had an impact on the interpretability of study results (ADSL, ADCORE, ADPD).

The FDA's Assessment:
The FDA clarifies that IPD refers to Important Protocol Deviations. In the ADPD dataset, there were 59 patients in the leukapheresed set with protocol deviations. One of these patients, USUBJID (b) (6) , had an important protocol deviation flag in the dataset related to procedures- specifically, the subject had second baseline scans (b) (6) before finishing bridging therapy on (b) (6) USUBJID (b) (6) did not have expected day 270 followup due to hospitalization for COVID-19. USUBJID (b) (6) did not complete a scheduled visit on April 10, 2022 and on April 30, 2022 due to COVID-19. Table 14.1.2.1 in the CSR (Summary of Protocol Deviations Leukapheresis Set) confirms that there was one important protocol deviation related to procedures and 2 subjects with at least one COVID-19 related protocol deviation. None of these deviations had any impact on manufacturing of the drug product.

Table of Demographic Characteristics

Data:

Table 1616: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67)
Age (Years) - n	67
Median	62.0
Min, Max	37, 81
Age group (Years) - n (%)	
< 65	37 (55.2)
≥ 65 - < 75	20 (29.9)
≥ 75	10 (14.9)
Sex - n (%)	
Female	28 (41.8)
Male	39 (58.2)
Ethnicity - n (%)[a]	
Hispanic or Latino	1 (1.5)
Not Hispanic or Latino	45 (67.2)
Not reported	21 (31.3)
Primary Race[b]	
Asian	4 (6.0)

Table 1616: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67)
Black or African American	1 (1.5)
White	38 (56.7)
Not Collected or Unknown	24 (35.8)
Region - n (%)	
Europe	31 (46.3)
Japan	2 (3.0)
North America	34 (50.7)
MZL Subtype (per Investigator) at screening - n (%)	
Extranodal MZL/MALT	17 (25.4)
Gastric involvement at screening, yes	1 (1.5)
Gastric involvement at screening, no	16 (23.9)
Nodal	32 (47.8)
Splenic	18 (26.9)
Time from initial diagnosis to liso-cel infusion (years) - n	67
Median	6.64
Min, Max	1.49, 23.84
Time since most recent relapse to liso-cel infusion (years) - n	67
Median	0.27
Min, Max	0.13, 4.09
≤ 6 months, n (%)	54 (80.6)
≤ 12 months, n (%)	63 (94.0)
Time from Completion of Most Recent Systemic Regimen to Progression (or SD if Missing Progression Date), months	
Median	1.77
Min, Max	-9.3, 81.8
Subjects Progressed or with SD before Regimen Completion, n (%)	14 (20.9)
≥ 0 - ≤ 6 Months, n (%)	28 (41.8)
> 6 - ≤ 12 Months, n (%)	11 (16.4)
POD24[c] - n (%)	
Yes	24 (35.8)
No	43 (64.2)
Refractory or Relapsed to last line of therapy per protocol[d] - n (%)	
Refractory	26 (38.8)
Relapsed	41 (61.2)
SPD prior to LDC per IRC (categorized) - n (%)	
≥ 50 cm^2	6 (9.0)
< 50 cm^2	56 (83.6)
Not reported	5 (7.5)
ECOG performance status at screening - n (%)	
0	37 (55.2)
1	30 (44.8)
LVEF at screening - n (%)	
≥ 40 to < 50%	2 (3.0)
≥ 50%	65 (97.0)
C-Reactive Protein prior to liso-cel infusion - n (%)	
< 20 mg/L	49 (73.1)
≥ 20 c mg/L	17 (25.4)

Table 1616: Applicant - Key Demographic and Baseline Characteristics - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67)
Not reported	1 (1.5)
LDH prior to LDC - n (%)	
≤ ULN	35 (52.2)
> ULN	32 (47.8)
Bulky disease (modified GELF[e]) at screening - n (%)	
Yes	15 (22.4)
No	52 (77.6)

[a] Ethnicity "Not reported" was 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] POD24 definition: progression of disease within 24 months of initiation of first-line chemoimmunotherapy with anti CD20 and alkylating agent.

[d] Refractory to last line of therapy defined as a best response of SD or PD after last line of therapy. Relapsed defined as relapse after an initial CR or PR to the last line of therapy.

[e] Per the modified GELF criteria, bulky disease is defined as any mass > 7 cm, or 3 or more masses (each > 3 cm) based on Investigator assessment.

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

Source: ADSL, ADCORE, ADDX

The Applicant's Position:

In the 3L+ MZL Liso-cel-treated Analysis Set (N = 67), disease characteristics were reflective of subjects with 3L+ MZL (Table 10). The study population represents the 3 MZL subtypes.

The FDA's Assessment:

For the 66 MZL patients included in FDA's primary efficacy analysis, the median age was 63 years (range: 37 to 81 years), 58% were male, Eastern Cooperative Oncology Group performance status was 0 in 55% and 1 in 45% of patients; 58% were White, 6% were Asian and 2% were Black. Two percent of patients were Hispanic. 84 percent of patients had Stage III to IV disease at study entry, 21% had bulky disease, 38% had refractory disease to the most recent regimen, and 35% had progression of disease within 24 months of initial diagnosis (POD24). The FDA notes that 48% of enrolled patients were from the US. The FDA also notes that the majority of patients enrolled had nodal MZL although nodal MZL is the least frequent MZL subtype. As previously noted, MZL patients enrolling on Cohort 4 of Study FOL-001 were not required to have an indication for systemic treatment for study enrollment (i.e. symptoms of threatened end-organ function, clinically significant or progressive cytopenias, clinically significant bulky disease, or rapidly progressive disease) and meeting one or more GELF criteria was not required for the MZL Cohort eligibility. In turn, 15% of patients had stage I to II disease, 77% had no B symptoms, 79% of patients did not have bulky disease, and 85% had a tumor burden less than 50 cm2 prior to initiation of lymphodepleting chemotherapy (measured by using the sum of the products of the longest perpendicular

diameters (SPD) as per Lugano criteria).

In general, demographic data as presented in Table 17 from the primary efficacy population and the cohort of all leukapheresed subjects with MZL demonstrates that the primary efficacy population was demographically similar to all subjects enrolled with MZL and subjects in the safety population.

Table 1717: FDA - FDA - Key Demographic and Baseline Characteristics

Demographics	**Safety Population n= 67**	**Efficacy Population n= 66**	**ITT Population N= 77**
Age			
Median	62	63	64
< 65	37 (55)	36 (55)	39 (51)
65-75	20 (30)	20 (30)	26 (34)
>75	10 (15)	10 (15)	12 (16)
Min, Max	37, 81	37, 81	37, 81
Sex			
Male	39 (58)	38 (58)	47 (61)
Female	28 (42)	28 (42)	30 (39)
Ethnicity			
Hispanic	1 (1.5)	1 (2)	3 (4)
Not Hispanic	45 (67)	45 (68)	50 (65)
Not Reported	21 (31)	20 (30)	24 (31)
Race			
Asian	4 (6)	4 (6)	4 (5)
Black	1 (1.5)	1 (2)	2 (3)
White	38 (57)	38 (58)	43 (56)
Unknown	24 (36)	23 (35)	28 (36)
Region			
Europe	31 (46)	30 (45)	35 (45)
Japan	2 (3)	2 (3)	2 (3)
North America	34 (51)	34 (52)	40 (52)
US	32 (48)	32 (48)	38 (49)
Canada	2 (3)	2 (3)	2 (2.6)
MZL Subtype			
Extranodal	17 (25)	17 (26)	19 (25)
Nodal	32 (48)	32 (48)	37 (48)
Splenic	18 (27)	17 (26)	21 (27)
Time from initial diagnosis to liso-cel infusion (years)	6.65 1.49, 23.84	6.78 1.49, 23.8	6.9 1.49, 23.8

Median Min, Max			
Time since most recent relapse to liso-cel infusion (years) Median Min, Max	0.27 0.13, 4.09	0.27 0.13, 4.09	0.27 0.13, 4.09
Time from completion of most recent systemic regimen to progression, months Median Min, Max	2.03 -9.3, 81.8	2.38 -9.3, 81.8	2.04 -9.3, 81.8
Stage 1 2 3 4	3 (4.4) 7 (10) 8 (12) 49 (73)	3 (4.4) 7 (10) 8 (12) 48 (72)	3 (4) 7 (9) 9 (12) 58 (75)
POD24 Yes No NE	24 (36) 43 (64) 0	23 (35) 43 (65) 0	25 (33) 50 (65) 2 (3)
Relapsed or refractory Relapsed Refractory	41 (61) 26 (39)	41 (62) 25 (38)	45 (58) 32 (42)
Double refractory Yes No	11 (16) 56 (84)	10 (15) 56 (85)	14 (18) 63 (82)
Bone marrow involvement Yes No Not reported	28 (42) 38 (57) 1 (1.5)	27 (41) 38 (58) 1 (2)	33 (43) 41 (53) 3 (4)
Gastric Involvement Yes No Not reported	1 (1.5) 16 (24) 50 (75)	1 (2) 16 (24) 49 (74)	1 (1) 18 (23) 58
SPD prior to LDC >50 cm2 < 50 cm2	6 (9) 56 (84)	6 (9) 56 (85)	58 6

Not reported	5 (7.5)	4 (6)	13
ECOG PS 0 PS 1	 37 (55) 30 (45)	 36 (55) 30 (45)	 41 (53) 36 (47)
Bulky at screening Yes No	 15 (22) 52 (78)	 14 (21) 52 (79)	 18 (23) 59 (77)
B symptoms No Yes	 52 (77) 15 (22)	 51 (77) 15 (22)	 57 (74) 20 (26)
FDG avid Yes No	 13 (19) 54 (81)	 13 (20) 53 (80)	 17 (22) 60 (78)
Source: FDA Analysis of ADSL, ADCMS, ADDX datasets -JCAR-FOL1-MZL cohort			

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

Data:

Table 1818: Applicant - Summary of Prior Anticancer Systemic Therapies - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67)
Number of prior systemic therapies	
Median	3.0
Min, Max	2, 12
Number of prior systemic therapies - n (%)	
2	30 (44.8)
3	16 (23.9)
4	7 (10.4)
≥ 5	14 (20.9)
Number of All Prior Radiotherapies	
N	67
Median	0.0
Min, Max	0, 7
Number of All Prior Radiotherapies, n (%)	
0	48 (71.6)
1	13 (19.4)
2	5 (7.5)
≥ 5	1 (1.5)
Type of last line of therapy prior to liso-cel, n (%)	
Systemic treatment only	48 (71.6)
Radiotherapy only	0
Both systemic treatment and radiotherapy	19 (28.4)

Table 1818: Applicant - Summary of Prior Anticancer Systemic Therapies - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ MZL (Cohort 4; N = 67)
Time from start of last systemic regimen prior to liso-cel, years	
Median	1.3
Min, Max	0.2, 9.2
Best response to last prior systemic regimen - n (%)	
CR	23 (34.3)
PR	17 (25.4)
SD	10 (14.9)
PD	17 (25.4)
Prior HSCT - n (%)	
Yes[a]	11 (16.4)
Autologous	11 (16.4)
Received Prior - n (%)	
PI3K inhibitors	6 (9.0)
Rituximab and lenalidomide (R2)	15 (22.4)
Bendamustine	52 (77.6)
BTKi at anytime[b]	26 (39.4)
BTKi in the last line[b]	16 (24.2)

Systemic therapy includes chemotherapy, immunotherapy and radioimmunotherapy.

[a] HSCT was grouped with preceding chemotherapy regimen and any intervening conditioning regimen, including radiation, and considered together as one line of therapy.

[b] Percentage based on Liso-cel-treated Efficacy Set (N = 66)

Source: ADSL, ADCORE, ADCM, ADCMS, ADPR

Table 1919: Applicant-Summary of Anticancer Therapies for Disease Control - Liso-cel-treated Analysis Set - Study FOL-001

	3L+ R/R MZL (Cohort 4; N = 67)
Anticancer Treatment	
Yes	30 (44.8)
No	37 (55.2)
Type of Treatment	
Systemic Treatment Only	26 (38.8)
Radiotherapy Only	3 (4.5)
Both systemic treatment and radiotherapy	1 (1.5)
Systemic Anticancer Medication for Disease Control	
Antineoplastic and Immunomodulating Agents (reported in ≥ 5% of subjects)	25 (37.3)
Rituximab	15 (22.4)
Cyclophosphamide	9 (13.4)
Gemcitabine	4 (6.0)
Vincristine	6 (9.0)
Oxaliplatin	4 (6.0)
Doxorubicin	4 (6.0)
Ibrutinib	4 (6.0)

Anticancer treatment for disease control is defined as any systemic therapy or radiation therapy provided to subjects for disease control after leukapheresis and prior to LDC.
The ATC term and preferred name are coded using WHODrug dictionary version WHODrug Global B3 March 2023 and listed in descending order of the frequency of ATC term and preferred name.
Source: ADSL, ADCORE, ADCM, ADCMS

The Applicant's Position:

In the MZL Cohort, the median number of prior systemic therapies (3; range: 2, 12) was reflective of a heavily pretreated R/R population. The median time from start of last systemic therapy prior to liso-cel administration was 1.3 years (Table 11). 22.4% had received rituximab with lenalidomide, 77.6% had received bendamustine, 9.0% had received a PI3K inhibitor, and 16.4% of subjects had prior autologous HSCT.

A total of 30 (44.8%) subjects received bridging therapy for disease control during the liso-cel manufacturing period. Of these, 26 subjects received systemic therapy only, 3 subjects received radiotherapy only, and 1 subject received both systemic and radiotherapy. The most commonly used bridging therapy was rituximab therapy (22.4% subjects). Per FDA feedback from the Type B pre-sBLA interaction held on 04-Apr-2025 (Meeting ID# 21150, Question 2 - Safety Analysis), post-hoc analyses were performed for the duration of bridging therapy for disease control. The median duration of systemic therapy was 12.0 (range: 1.0 to 81.0) days and the median duration of radiotherapy was 4.0 (range: 2.0 to 15.0) days (ADCM, ADPR).

The FDA's Assessment:

The FDA acknowledges that the median number of prior treatments was 3 (range 2, 12). However, MZL is a multiply relapsing disease, and the relapses are generally treatable such that the number of prior treatments (i.e. 3) does not necessarily correlate with an aggressive phenotype. In fact, within the efficacy population, only 38% had refractory disease, 15% had double refractory disease, and 35% had POD24 disease. At screening, fourteen percent of patients had stage 1-2 disease, 79% did not have bulky disease, and 77% did not have B symptoms. Finally, the FDA notes that 23% of patients had received prior lenalidomide and rituximab (R2) and 14% had received prior Zanubrutinib which are both FDA-approved therapies in MZL.

Table 20 includes baseline disease characteristics for 66 subjects with MZL included in the primary efficacy analysis and the 77 subjects with MZL who were leukapheresed to allow comparison between the two groups. There were no major differences between the efficacy population and leukapheresed population likely to impact study findings.

Table 2020: FDA - Summary of Prior Anticancer Therapies

	Safety Population n= 67	**Efficacy Population n= 66**	**ITT Population N= 77**
Number of prior systemic therapies Median Min, Max	3 2, 12	3 2, 12	3 2, 12
Prior Splenectomy for Splenic MZL Yes No	5 (7.5) 62 (92.5)	5 (7.6) 61 (92.4)	6 (7.8) 71 (92.2)
Prior HSCT Yes No	11 (16.4) 56 (84)	11 (16.7) 55 (83.3)	11 (14.2) 66 (85.7)
Number of All Prior Radiotherapies Median Min, Max 0 1 2 >3	0 0, 7 48 (72) 13 (19) 5 (7.5) 1 (1.5)	0 0, 7 47 (71.2) 13 (19.7) 5 (7.6) 1 (1.5)	0 0, 7 56 (73) 14 (18) 6 (7.8) 1 (1.3)

Best response prior to last prior systemic regimen CR PR SD PD NE	 23 (34) 17 (25) 10 (14.9) 17 (25) 0	 23 (34.8) 17 (25.8) 16 (24.2) 10 (15.2) 0	 25 (32.4) 19 (24.7) 13 (16.9) 19 (24.7) 1 (1.3)
Received prior therapies PI3K R2 Bendamustine BTK NX2127 Acalabrutinib Ibrutinib Pirtobrutinib Zanubrutinib Tirabrutinib	 6 (9) 15 (22) 52 (77.6) 1 (1.5) 3 (4.5) 26 (38.8) 6 (9) 9 (13.4) 0 (0)	 6 (9) 15 (22.7) 51 (77.2) 1 (1.5) 3 (4.5) 25 (37.9) 6 (9) 8 (12) 0	 4 (5.2) 15 (19.5) 61 (79.2) 2 (2.6) 3 (3.9) 32 (41.6) 7 (9.1) 10 (14.9) 1
Anticancer treatment Yes No	 30 (44.8) 37 (55.2)	 29 (43.9) 37 (56)	 34 (44) 43 (56)
Systemic Anticancer Medication for Disease Control Anti-CD20 Steroids Nitrogen mustard Pyrimidine Analog Vinca alkaloids Platinum Doxorubicin BTK inhibitor Venetoclax Folic Acid Analog Lenalidomide Podophyllotoxin PI3K	 18 (26.9) 12 (17.9) 12 (17.9) 5 (7.5) 6 (9) 5 (7.5) 4 (6) 6 (9) 1 (1.5) 1 (1.5) 3 (4.5) 0 0	 17 (26) 12 (18) 11 (17) 5 (8) 5 (8) 5 (8) 3 (4.5) 5 (7.6) 0 1 (1.5) 3 (4.6) 0 0	 20 (25.9) 13 (16.9) 15 (19.5) 5 (6.5) 7 (9.1) 5 (6.5) 6 (7.8) 8 (10.4) 1 (1.3) 1 (1.3) 3 (3.9) 1 (1.3) 1 (1.3)
Source: FDA analysis of ADCMS and ADCMDatasets			

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Concomitant Medications: In the Liso-cel-treated Analysis Set, 67 (100.0%) subjects received at least one concomitant medication and the most frequently prescribed

medications by ATC term were for nervous system (67 [100%] subjects; most commonly paracetamol in 65 [97%]), alimentary tract and metabolism (66 [98.5%] subjects; most commonly ondansetron in 44 [65.7%]), anti-infectives for systemic use (66 [98.5%] subjects; most commonly sulfamethoxazole/trimethoprim in 48 [71.6%]), and respiratory system (63 [94.0%] subjects; diphenhydramine in 22 [32.8%]) (ADSL, ADCORE, 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 medications/procedures as specified in the protocol, and were reflective of the underlying medical conditions and consistent with those expected to be used for the management of AEs that were reported in the study.

The FDA's Assessment:
Out of 77 patients who underwent leukapheresis, 31 (40%) received bridging therapy for disease stabilization prior to liso-cel treatment.

Table provides the therapies administered as bridging therapies (i.e. systemic anti-cancer medication for disease control).

Table 2121: FDA - Bridging Therapy Administered in Study JCAR-FOL-001 MZL Cohort

CMDECOD	All leukapheresed, n (%) 31/77 (40%))	Primary efficacy population, n (%) 27/66 (41%)
RITUXIMAB	17 (22%)	15 (23)
CYCLOPHOSPHAMIDE	11 (14	9 (14)
PREDNISONE	8 (10)	7(11)
VINCRISTINE	7 (9)	6 (9)
DOXORUBICIN	6 (8)	4 (6)
IBRUTINIB	5 (6)	4 (6)
DEXAMETHASONE	4 (5)	3 (5)
GEMCITABINE	4 (5)	4 (6)
OXALIPLATIN	4 (5)	4 (6)
BENDAMUSTINE	3 (4)	3 (5)
LENALIDOMIDE	3 (4)	3 (5)
OBINUTUZUMAB	3 (4)	3 (5)
PREDNISONE	2 (3)	2 (3)
ZANUBRUTINIB	2 (3)	1 (2)
CISPLATIN	1 (1)	1 (2)
CYTARABINE	1 (1)	1 (2)
ETOPOSIDE	1 (1)	0 (0)

IFOSFAMIDE	1 (1)	0 (0)
METHOTREXATE	1 (1)	1 (2)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (1)	1 (2)
PIRTOBRUTINIB	1 (1)	1 (2)
UMBRALISIB	1 (1)	0 (0)
VENETOCLAX	1 (1)	1 (2)
Source: FDA Analysis of ADCM data- JCAR-FOL-001 MZL Cohort		

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 2222: Applicant - ORR per IRC and Sensitivity Analyses - 3L+ MZL - Study FOL-001

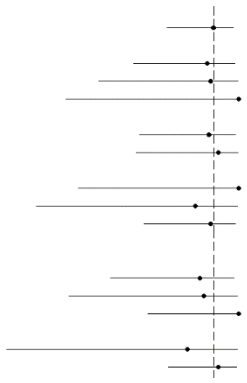
	3L+ MZL (Cohort 4)
ORR per IRC (Liso-cel-treated Efficacy Analysis Set)	N = 66
n (%)	63 (95.5)
95% CI[a]	(87.3, 99.1)
Sensitivity Analyses	
ORR per Investigator (Liso-cel-treated Efficacy Analysis Set)	N = 66
n (%)	63 (95.5)
95% CI[a]	(87.3, 99.1)
ORR per IRC (Leukapheresed [ITT] Analysis Set)	N = 77
n (%)	65 (84.4)
95% CI[a]	(74.4, 91.7)

[a] Based on exact Clopper-Pearson method.

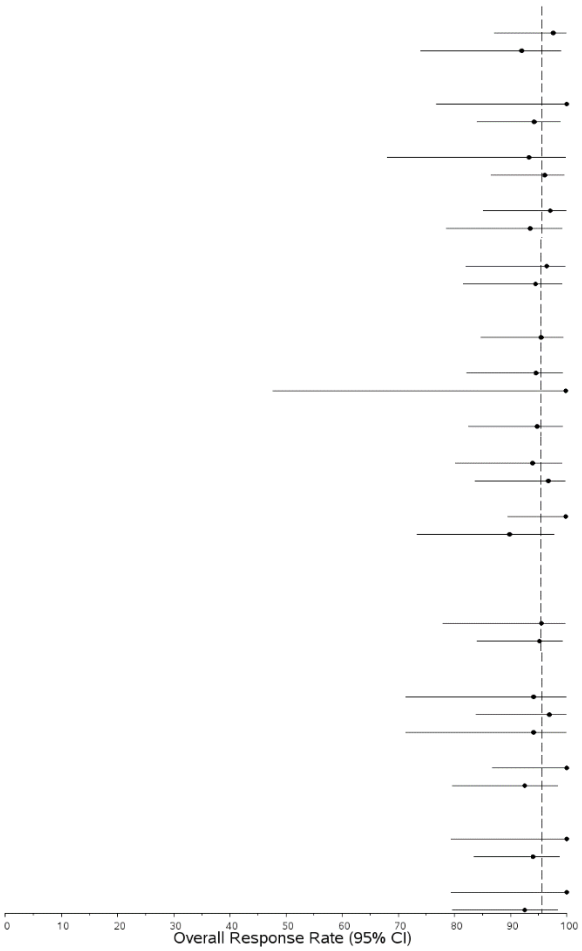
Source: ADSL, ADCORE, ADRS

Figure 2: Applicant - Forest Plot of ORR Subgroup Analysis per IRC - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL - Study FOL-001

Group	N of Responders (N of Subjects)	ORR (95% Exact CI)
OVERALL	63 (66)	95.5% (87.3, 99.1)
AGE		
< 65	34 (36)	94.4% (81.3, 99.3)
>= 65 AND < 75	19 (20)	95.0% (75.1, 99.9)
>= 75	10 (10)	100.0% (69.2, 100.0)
SEX		
MALE	36 (38)	94.7% (82.3, 99.4)
FEMALE	27 (28)	96.4% (81.7, 99.9)
FLIPI		
LOW (0-1)	11 (11)	100.0% (71.5, 100.0)
INTERMEDIATE (2)	12 (13)	92.3% (64.0, 99.8)
HIGH (3-5)	38 (40)	95.0% (83.1, 99.4)
NUMBER OF PRIOR SYSTEMIC LINES OF THERAPIES		
2	27 (29)	93.1% (77.2, 99.2)
3	15 (16)	93.8% (69.8, 99.8)
>= 4	21 (21)	100.0% (83.9, 100.0)
PRIOR ASCT		
YES	10 (11)	90.9% (58.7, 99.8)
NO	53 (55)	96.4% (87.5, 99.6)



RELAPSED VS REFRACTORY		
RELAPSED	40 (41)	97.6% (87.1, 99.9)
REFRACTORY	23 (25)	92.0% (74.0, 99.0)
BULKY DISEASE (MODIFIED GELF) AT SCREENING		
YES	14 (14)	100.0% (76.8, 100.0)
NO	49 (52)	94.2% (84.1, 98.8)
PRIOR R2 USE		
YES	14 (15)	93.3% (68.1, 99.8)
NO	49 (51)	96.1% (86.5, 99.5)
LDH AT PRE-LDC		
<= ULN	34 (35)	97.1% (85.1, 99.9)
> ULN	29 (31)	93.5% (78.6, 99.2)
BRIDGING THERAPY		
YES	28 (29)	96.6% (82.2, 99.9)
NO	35 (37)	94.6% (81.8, 99.3)
ETHNICITY		
HISPANIC OR LATINO	1 (1)	N.A.
NOT HISPANIC OR LATINO	43 (45)	95.6% (84.9, 99.5)
RACE		
WHITE	36 (38)	94.7% (82.3, 99.4)
NON-WHITE	5 (5)	100.0% (47.8, 100.0)
ASIAN	4 (4)	N.A.
NON-ASIAN	37 (39)	94.9% (82.7, 99.4)
GCSF		
YES	32 (34)	94.1% (80.3, 99.3)
NO	31 (32)	96.9% (83.8, 99.9)
REGION		
NORTH AMERICA	34 (34)	100.0% (89.7, 100.0)
EUROPE	27 (30)	90.0% (73.5, 97.9)
JAPAN	2 (2)	N.A.
PROGRESSION WITHIN 24 MONTHS OF 1ST LINE THERAPY WITH ANTICD20 AND ALKYLATOR		
YES	22 (23)	95.7% (78.1, 99.9)
NO	41 (43)	95.3% (84.2, 99.4)
MARGINAL ZONE LYMPHOMA SUBTYPE		
EXTRANODAL OF MALT	16 (17)	94.1% (71.3, 99.9)
NODAL	31 (32)	96.9% (83.8, 99.9)
SPLENIC	16 (17)	94.1% (71.3, 99.9)
PRIOR BTKI AT ANYTIME		
YES	26 (26)	100.0% (86.8, 100.0)
NO	37 (40)	92.5% (79.6, 98.4)
PRIOR BTKI IN THE LAST LINE		
YES	16 (16)	100.0% (79.4, 100.0)
NO	47 (50)	94.0% (83.5, 98.7)
PRIOR BTKI		
IN THE LAST LINE	16 (16)	100.0% (79.4, 100.0)
NO BTKI	37 (40)	92.5% (79.6, 98.4)



Two-sided 95% CI based on exact Clopper-Pearson method.

ORR difference is not computed for subsets with < 5 subjects per analysis group.

Per the modified GELF criteria, bulky disease is defined as any mass > 7 cm, or 3 or more masses (each > 3 cm) at screening based on Investigator assessment.

Source: ADSL, ADCORE, ADSUB, ADRS

The Applicant's Position:

The primary efficacy endpoint of ORR (CR or PR) per IRC in 3L+ MZL Liso-cel-treated Efficacy Analysis Set was 95.5% (95% CI: 87.3, 99.1) (data cutoff: 29-Nov-2024; median follow-up 24.08 [min, max: 1.1, 43.0] months) (Table 13). The sensitivity analysis of ORR per Investigator assessment was consistent with the primary analysis. The ORR in the Leukapheresed (ITT) Analysis Set was lower than in the Liso-cel-treated Efficacy Analysis Set, which was an expected finding given that Leukapheresed (ITT) Analysis Set comprised all subjects who underwent leukapheresis, including those who did not receive liso-cel (10 subjects) and subjects who received liso-cel but did not have imaging for assessment of measurable disease completed after bridging therapy and prior to LDC (1 subject).

ORR was consistent across all subgroups evaluated (Figure 2).

The FDA's Assessment:

The primary endpoint in the original version of the protocol dated November 11, 2019 was complete response rate as assessed by CT using Lugano criteria (Cheson 2014). The primary endpoint was changed to overall response rate with Amendment 1 on July 6, 2021 at which time 116 subjects were already enrolled on Study FOL-001.

Response assessment occurred per the IRC charter dated September 11, 2022 which indicated that radiographic assessment would occur with two different radiologists independently reading each study subject. If there was no discordance, results from the first radiology read would be used. If there was discordance, adjudication would be performed by a radiologist who was not involved in the primary radiology review and who was blinded to the identity of the two primary readers. The adjudicator reviewed but did not reread the two primary reads and would choose the read felt to most accurately represent the prespecified adjudication variables, i.e. CT and CNS Best Response, CT and CNS Date of Progression, and CT and CNS Date of First Response.

Table 23 below summarizes the efficacy data for 66 efficacy evaluable MZL subjects who met duration of follow up criteria (i.e. at least 9 months of DOR follow up) and for 77 leukapheresed patients using IRC assessed response per Lugano criteria. FDA Preliminary Meeting Comments generated 10/10/2024 (CRMTS 20603) indicated that the primary analysis should take place when at least 60 patients had been followed for DOR for a minimum of 12 months after first response as assessed by IRC. However, the FDA will accept at least 9 months of DOR follow up in this indolent lymphoma. DOR follow up begins at the time of first objective disease response, not the first disease assessment.

The ORR was high in both the primary efficacy population and the leukapheresed population, albeit slightly lower in the leukapheresed population. The ORR is favorable in R/R MZL and is supported by duration of response and safety as described below and in section 8.2.

Table 2323: FDA - Response Rates in Subjects with R/R MZL Treated with Liso-cel in Study FOL-001

Response rate	**Primary Efficacy Population n= 66**	**All Leukapheresed Patients n=77**
Overall Response Rate, n (%)	63 (95.5)	65 (84.4)
[95% CI]	[87.3, 99.1]	[74.4, 91.7]
Complete Response Rate	41 (62.1)	43 (55.8)
[95% CI]	[49.3, 73.8]	[44.1, 67.2]
Partial Response Rate	22 (33.3)	22 (28.6)

[95% CI]	[22.2, 46.0]	[18.8, 40.0]
Source: FDA Analysis of ADRS data- JCAR-FOL-001 and FDA statistical reviewer's memo		

Table 24 captures the 14 discrepancies between the best overall response rate in the efficacy population as assessed by the Investigator and the IRC as well as the Applicant's response to an FDA Information Request dated August 25, 2025. The Applicant previously noted that IRC radiologist 1 was the accepted radiologist except as noted below when IRC radiologist 2 was the accepting radiologist. The FDA notes that Lugano 2014 criteria require that for a CT-based CR, non-measured lesions are absent whereas the presence of non-measured lesions on PET/CT are considered not applicable. Lugano 2014 also requires that organ enlargement regresses to normal (i.e. less than 13 cm). In reviewing the ADRS and ADTR datasets, the FDA agreed with the IRC assessment in 9 out of the 14 discrepancies. The remaining 5 discrepancies still favor the assessment made by the IRC given the Applicant's adherence to the IRC charter.

Table 24 : FDA – FDA Adjudication of Discrepant Best Overall Response Rate

USUBJID	Histology	BOR IRC	BOR INV	Applicant Response
(b) (6)	Splenic MZL	CR	PR due to persistence of non-target lesions 4 on PET/CT at month 36.	IRC radiologist 1 evaluated response on PET/CT and noted PR at day 29 and CR by month 3 which was maintained through month 36 when two different non-measured lesions resolved.
	Nodal MZL	CR	PR due to persistence of 2 non-target lesions on PET/CT at D730.	IRC radiologist 1 evaluated response on CT and PET/CT and noted CR at day 29 which was maintained through day 730 (i.e. no non-target lesions seen).
	Nodal MZL	CR	PR due to persistence of a 1.6 cm target lesion and 2 non-target lesions at day 90 on PET/CT.	IRC radiologist 1 used PET/CT and noted a PR at day 29 followed by a CR at month 3 maintained through day 90 with resolution of one target and one non-target lesion. The subject progressed at day 180.
	Splenic MZL	CR	PR due to persistence of a 1.6 cm target lesion and a 13.3 cm spleen at day 730 on PET/CT.	IRC Radiologist 1 noted a PR on CT at month 3 and a CR at month 24. The target lesion and spleen reduced to 12.6 cm on day 730. IRC Radiologist 2 noted reduction in spleen size to 13.2 cm and noted a PR at month 24.
	Splenic MZL	CR	PR based on 14.6 cm spleen on CT on day 730 .	IRC radiologist 1 noted a PR on CT at day 29 (spleen 16 cm) which converted to a CR at day 180 (12 cm) and measured 10.5 cm at day 730. IRC radiologist 2

(b) (6)

			noted a PR at day 29 (16.5 cm) that persisted through day 730 (spleen measured 13 cm).
Nodal MZL	CR	PR due to persistence of target lesions (3 lesions measuring 1 cm each) at month 36 on PET/CT.	IRC radiologist 1 noted a CR at day 29 on CT which was maintained through month 36 when there was resolution of all target lesions and a spleen diameter of 10 cm.
Splenic MZL	CR	PR due to persistence of 3 target lesions (1.6 cm, 1.7 cm, and 2.2 cm) and one non-target lesion on PET/CT at day 545.	IRC radiologist 2 was the accepted radiologist and noted a PR on CT from day 29 through month 12. A CR was noted at month 18 with a reduction of 3 target lesions to < 1.5 cm and no nontarget lesion on CT at 18 months. (IRC radiologist 1 noted a PR at day 90 and a CR at month 12 that was maintained through month 24 with one residual target lesion measuring 1.5 cm).
Nodal MZL	CR	PR due to GCSF administration causing spleen enlargement to 14.7 cm and persistence of non-target lesions on PET/CT at day 730.	IRC radiologist 1 noted a PR at day 29 and month 3 and a CR by month 6 maintained through month 24. IRC radiologist 1 measured the spleen at 12.4 cm at month 6 and 13.5 cm on CT on day 730 due to intermittent GCSF administration between June 2022 and August 2024. IRC radiologist 2, however, noted a PR at day 29 (spleen 12.4 cm), SD at month 3 (spleen 13.9 cm), a CR between month 6-12, PD at month 18 (spleen 14.6 cm), and stable disease at month 24 (13.9 cm).
Splenic MZL	CR	PR due to 1.8 cm and 1.5 cm target lesion on day 730 on CT.	IRC radiologist 2 was the accepted radiologist and noted a PR on CT since day 29 until month 24 when a CR was determined though a 1.5 cm target lesion remained . IRC radiologist 1 noted a PR from day 29 onward with a residual target lesion measuring 2.2 cm remaining at day 730.
Extranodal MZL	CR	PR due to 14 cm spleen. Imaging modality used at month 30 was not provided.	Target lesion 1 (T01) was not evaluable due to an incomplete imaging technique between month 3 and month 24 . IRC radiologist 1 noted SD at day 29 (spleen 11.7 cm and T01 1.6 cm) on PET/CT and a CR at month 30 on CT (spleen 11.9 cm and T01 0 cm). IRC radiologist 2 noted a PR at day 29 on CT (spleen 13.2 cm and 2 target lesions measuring 0 and 1.6 cm) and a CR at month 30 (spleen 12.5 cm and no target lesions).
Nodal MZL	CR	Reason for PR on CT at day 730 is unclear	IRC radiologist 1 noted a PR at day 29 and a CR at month 9 (resolution of 2

(b) (6)			(all 6 target lesions resolved and spleen measured 8.2 cm).	target lesions on CT and spleen 4.5 cm). D730, 2 non-target lesions were still resolved and spleen measured 4.6 cm).
	Nodal MZL	CR	PR based on a 1.8 cm target lesion at day 270 and 2 non-target lesions on CT.	IRC radiologist 1 identified a single target lesion measuring 2.0 cm at baseline which improved to 1.1 cm on day 270 on CT. IRC radiologist 2 noted a 2.5 cm lesion and a 2.1 cm lesion. Both lesions were not measurable at day 270.
	Splenic MZL	CR	PR based on presence of a 13.6 cm spleen and one non-target lesion on CT.	IRC radiologist 1 identified a 21 cm spleen at baseline on CT which reduced to 12.5 cm spleen on CT at month 12. Radiologist 2 noted a 22.2 cm spleen at baseline which reduced to 12.2 cm at 12 months.
	Extranodal MZL	CR	PR based on 1.9 cm target lesion on PET/CT at month 36.	IRC radiologist 1 noted 5 lesions at baseline: 5.5 cm, 6.4 cm, 3.6 cm, 6.6 cm, and 3.6 cm on CT. At month 36, lesions had decreased to 1 cm, 0.5 cm, 0 cm, 0 cm, and 0.5 on CT. IRC radiologist 2 noted 3 target lesions on PET/CT (6.2 cm, 6.5 cm, and 8.1 cm). My month 12, only the spleen remained at 12.6 cm on PET/CT.

The FDA notes that five patients with bone marrow involvement at the time of screening did not have posttreatment bone marrow biopsies (see table 25 below). However, none of these patients were determined to have a CR (i.e. 4 of these patients' responses were assessed as partial remissions and one was assessed as progressive disease). Finally, the single patient out of 17 patients with extranodal MZL with gastric involvement at baseline (i.e. USUBJID (b) (6) was determined to have a partial response.

Table 25 : FDA - FDA Review of Bone Marrow Involvement to confirm CR

USUBJID	Baseline BMB	BMB Status at Time of CR
(b) (6)	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Response assessment was PR; no bone marrow biopsy was completed
	Involved (b) (6)	Negative (b) (6)
	Involved	Negative

(b) (6)	(b) (6)	(b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Response assessment was PR; no bone marrow biopsy was completed
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Response assessment was PR; no bone marrow biopsy was completed
	Involved (b) (6)	Response assessment was PD; no bone marrow biopsy was completed
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Inadequate sample (b) (6) Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative (b) (6)
	Involved (b) (6)	Negative

(b) (6)		(b) (6)
	Involved (b) (6)	Response assessment was PD; no bone marrow biopsy was completed
Source: FDA analysis of ADBM data- JCAR-FOL-001 MZL cohort		

As noted in Table 26, no substantial differences in ORR were noted across subgroups. Since the Applicant is seeking an approval in MZL after 2 or more lines of therapy and since R2 has regular approval in previously treated marginal zone lymphoma in combination with a rituximab product, it is worth mentioning that on subgroup analysis the response rate among the 14 patients previously treated with R2 (ORR 93.3% (68.1, 99.8)) was similar to the response rate observed in the primary efficacy population (though the sample size was admittedly small). The response rate among patients previously treated with a Bruton tyrosine kinase inhibitor as a class is not clinically meaningful without extracting the response rate among patients previously treated with zanubrutinib which is under accelerated approval for patients with relapsed or refractory MZL who have received at least one anti-CD20 directed regimen. The review team was unable to estimate the ORR specifically for the Zanubrutinib treated population. Finally, the review team notes comparable response rates among relapse or refractory MZL patients treated with liso-cel regardless of the number of prior systemic therapies received.

Table 26 : FDA - Objective Response Rate in the Liso-cel Treated Analysis Set by Subgroups

Group	**N of Responders (N of Subjects)**	**ORR (95% Exact CI)[a]**
Overall	63 (66)	95.5% (87.3, 99.1)
Age		
< 65	34 (36)	94.4% (81.3, 99.3)
≥ 65 to < 75	19 (20)	95.0% (75.1, 99.9)
≥75	10 (10)	100% (69.2, 100)
Sex		
Female	27 (28)	96.4% (81.7, 99.9)
Male	36 (38)	94.7% (82.3, 99.4)
Ethnicity		
Hispanic or Latino	1 (1)	NA[b]
Not Hispanic or Latino	43 (45)	95.6% (84.9, 99.5)
Not Reported	19 (20)	95.0% (75.1, 99.9)
Race		
White	36 (38)	94.7% (82.3, 99.4)
Non-White	5 (5)	100 (47.8, 100)
Not Reported	22 (23)	95.7 (78,1, 99.9)
Race		
Asian	4 (4)	NA
Not Asian	37 (39)	94.9 (82.7, 99.4)

Not Reported	22 (23)	95.7 (78.1, 99.9)
Region		
N. America	34 (34)	100 (89.7, 100)
Europe	27 (30)	90 (73.5, 97.9)
Japan	2 (2)	NA
MZL Subtype per INV at Screening		
Extranodal MZL/MALT	16 (17)	94.1 (71.3, 99.9)
Nodal MZL	31 (32)	96.9 (83.8, 99.9)
Splenic MZL	16 (17)	94.1 (71.3, 99.9)
Number of Prior Systemic Therapies		
2	27 (29)	93.1 (77.2, 99.2)
3	15 (16)	93.8 (69.8, 99.8)
≥4	21 (21)	100 (83.9, 100)

[a]95% CI based on exact Clopper-Pearson method.
[b]ORR difference is not computed for subsets with < 5 subjects per analysis group.
(Source: Adapted from BLA 125714/644 Module 5.3.5, FDA reviewer's summary)

Data Quality and Integrity

The Applicant's Position:
Data review and quality control checks were implemented by the Applicant 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 Applicant'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 Applicant, 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

Per SAP, the primary analysis of the time-to-event endpoints DOR and PFS per IRC was based on EMA censoring rules. In this document, the DOR and PFS sensitivity

analyses per IRC based on FDA censoring rules are presented.

Data:

Table 2727: Applicant - Summary of Secondary Efficacy Endpoints - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL - Study FOL-001

	Liso-cel-treated Efficacy Analysis Set (N = 66)		Leukapheresed (ITT) Analysis Set (N = 77)
	Per IRC	Per Investigator Assessment	Per IRC
CRR			
N (%)	41 (62.1)	31 (47.0)	43 (55.8)
95% CI[a]	(49.3, 73.8)	(34.6, 59.7)	(44.1, 67.2)
PRR			
N (%)	22 (33.3)	32 (48.5)	22 (28.6)
95% CI[a]	(22.2, 46.0)	(36.0, 61.1)	(18.8, 40.0)
DOR, months[f]	N = 63	N = 63	N = 65
Median (95% CI)[b]	NA (25.59, NA)	NA (33.94, NA)	NA (25.59, NA)
Min, Max[c]	0.0+, 35.3+	2.0, 35.3+	0.0+, 35.3+
Median follow-up (from first response), months (95% CI)[d]	21.59 (17.28, 22.77)	22.74 (18.37, 23.03)	22.31 (17.28, 22.97)
Continued Response Rate, % (95% CI)[e]			
6 months	98.4 (88.9, 99.8)	96.8 (87.9, 99.2)	98.4 (89.3, 99.8)
12 months	96.7 (87.3, 99.2)	93.7 (84.0, 97.6)	96.8 (87.7, 99.2)
18 months	94.6 (84.1, 98.2)	91.8 (81.3, 96.5)	94.8 (84.6, 98.3)
24 months	90.1 (73.1, 96.6)	86.4 (68.2, 94.6)	88.0 (71.6, 95.2)
DOR if BOR is CR, months[f]	N = 41		N = 43
Median (95% CI)[b]	NA (24.48, NA)		NA (24.48, NA)
Min, Max[c]	0.0+, 35.3+		0.0+, 35.3+
Continued Response Rate, % (95% CI)[e]			
6 months	97.5 (83.5, 99.6)		97.6 (84.3, 99.7)
12 months	94.9 (81.2, 98.7)		95.2 (82.1, 98.8)
18 months	94.9 (81.2, 98.7)		95.2 (82.1, 98.8)
24 months	89.0 (66.6, 96.7)		86.4 (65.6, 95.0)
DOR if BOR is PR, months[f]	N = 22		N = 22
Median (95% CI)[b]	25.59 (25.59, NA)		25.59 (25.59, NA)
Min, Max[c]	2.0+, 32.8+		2.0+, 32.8+
Continued Response Rate, % (95% CI)[e]			
6 months	100 (100.0, 100.0)		100 (100.0, 100.0)
12 months	100 (100.0, 100.0)		100 (100.0, 100.0)
18 months	93.3 (61.3, 99.0)		93.3 (61.3, 99.0)
24 months	93.3 (61.3, 99.0)		93.3 (61.3, 99.0)
PFS[f]			
Events, n (%)	10 (15.2)	11 (16.7)	18 (23.4)
Median (95% CI)[b], months	NA (34.76, NA)	NA (34.76, NA)	NA (27.43, NA)
Min, Max[c], months	0.7, 36.6+	1.1, 36.6+	0.0+, 39.6+
PFS rate, % (95% CI)[e]			

Table 2727: Applicant - Summary of Secondary Efficacy Endpoints - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL - Study FOL-001

	Liso-cel-treated Efficacy Analysis Set (N = 66)		Leukapheresed (ITT) Analysis Set (N = 77)
	Per IRC	Per Investigator Assessment	Per IRC
6 months	93.9 (84.6, 97.7)	92.4 (82.8, 96.8)	89.3 (79.8, 94.5)
12 months	92.3 (82.6, 96.7)	90.9 (80.9, 95.8)	86.6 (76.6, 92.6)
18 months	90.5 (80.1, 95.6)	87.4 (76.4, 93.5)	82.3 (71.4, 89.3)
24 months	87.1 (73.5, 94.0)	87.4 (76.4, 93.5)	80.2 (68.7, 87.9)
Median follow-up (from infusion), months (95% CI)[d]	23.79 (19.35, 24.08)	23.85 (23.43, 24.15)	25.53 (21.68, 26.41)
OS			
Events, n (%)	9 (13.6)		16 (20.8)
Median (95% CI)[b], months	NA		NA
Min, Max[c], months	1.1, 43.0+		0.8, 44.2+
OS rate, % (95% CI)[e]			
6 months	97.0 (88.4, 99.2)		90.9 (81.9, 95.6)
12 months	95.5 (86.6, 98.5)		89.6 (80.3, 94.7)
18 months	90.4 (79.8, 95.6)		82.8 (72.2, 89.6)
24 months	90.4 (79.8, 95.6)		82.8 (72.2, 89.6)
Median follow-up (from infusion), months (95% CI)[d]	24.48 (23.72, 29.47)		26.02 (24.94, 31.18)

[a] Based on exact Clopper-Pearson method.

[b] Estimated from Kaplan-Meier product-limit estimates.

[c] Symbol '+' indicates a censored value.

[d] Reverse K-M method used to obtain the median follow-up and its 95% CI.

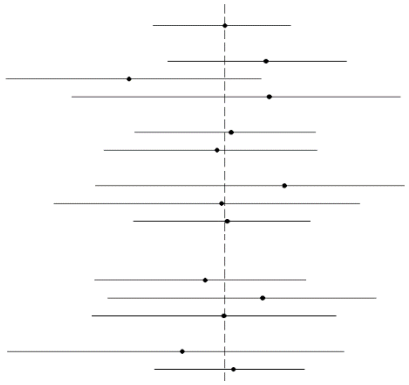
[e] Based on K-M estimates.

[f] Per FDA censoring rules

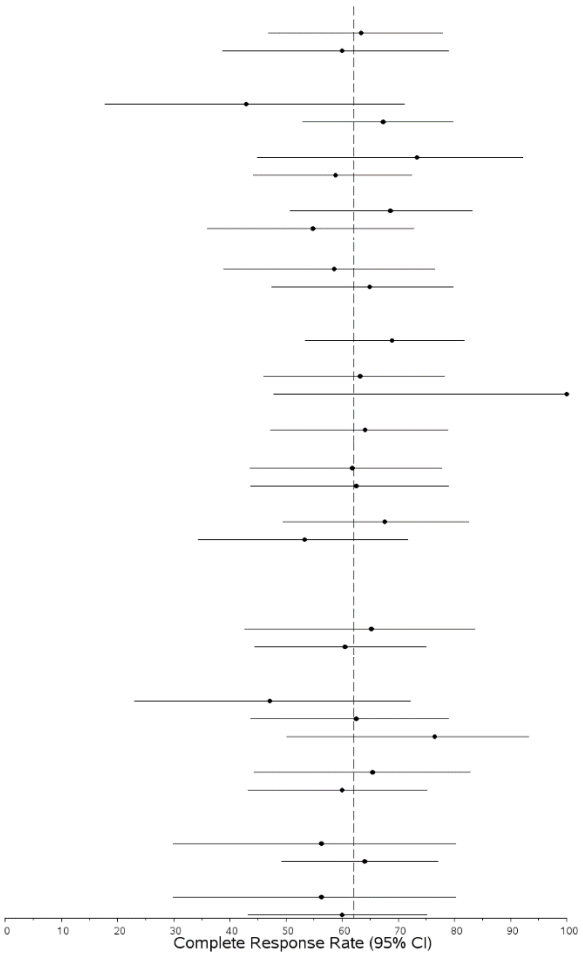
Source: ADSL, ADCORE, ADRS, ADTTE

Figure 3: Applicant - Forest Plot of CRR Subgroup Analysis per IRC - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL - Study FOL-001

Group	N of Responders (N of Subjects)	CRR (95% Exact CI)
OVERALL	41 (66)	62.1% (49.3, 73.8)
AGE		
< 65	25 (36)	69.4% (51.9, 83.7)
>= 65 AND < 75	9 (20)	45.0% (23.1, 68.5)
>= 75	7 (10)	70.0% (34.8, 93.3)
SEX		
MALE	24 (38)	63.2% (46.0, 78.2)
FEMALE	17 (28)	60.7% (40.6, 78.5)
FLIPI		
LOW (0-1)	8 (11)	72.7% (39.0, 94.0)
INTERMEDIATE (2)	8 (13)	61.5% (31.6, 86.1)
HIGH (3-5)	25 (40)	62.5% (45.8, 77.3)
NUMBER OF PRIOR SYSTEMIC LINES OF THERAPIES		
2	17 (29)	58.6% (38.9, 76.5)
3	11 (16)	68.8% (41.3, 89.0)
>= 4	13 (21)	61.9% (38.4, 81.9)
PRIOR ASCT		
YES	6 (11)	54.5% (23.4, 83.3)
NO	35 (55)	63.6% (49.6, 76.2)



RELAPSED VS REFRACTORY		
RELAPSED	26 (41)	63.4% (46.9, 77.9)
REFRACTORY	15 (25)	60.0% (38.7, 78.9)
BULKY DISEASE (MODIFIED GELF) AT SCREENING		
YES	6 (14)	42.9% (17.7, 71.1)
NO	35 (52)	67.3% (52.9, 79.7)
PRIOR R2 USE		
YES	11 (15)	73.3% (44.9, 92.2)
NO	30 (51)	58.8% (44.2, 72.4)
LDH AT PRE-LDC		
<= ULN	24 (35)	68.6% (50.7, 83.1)
> ULN	17 (31)	54.8% (36.0, 72.7)
BRIDGING THERAPY		
YES	17 (29)	58.6% (38.9, 76.5)
NO	24 (37)	64.9% (47.5, 79.8)
ETHNICITY		
HISPANIC OR LATINO	0 (1)	N.A.
NOT HISPANIC OR LATINO	31 (45)	68.9% (53.4, 81.8)
RACE		
WHITE	24 (38)	63.2% (46.0, 78.2)
NON-WHITE	5 (5)	100.0% (47.8, 100.0)
ASIAN	4 (4)	N.A.
NON-ASIAN	25 (39)	64.1% (47.2, 78.8)
GCSF		
YES	21 (34)	61.8% (43.6, 77.8)
NO	20 (32)	62.5% (43.7, 78.9)
REGION		
NORTH AMERICA	23 (34)	67.6% (49.5, 82.6)
EUROPE	16 (30)	53.3% (34.3, 71.7)
JAPAN	2 (2)	N.A.
PROGRESSION WITHIN 24 MONTHS OF 1ST LINE THERAPY WITH ANTICD20 AND ALKYLATOR		
YES	15 (23)	65.2% (42.7, 83.6)
NO	26 (43)	60.5% (44.4, 75.0)
MARGINAL ZONE LYMPHOMA SUBTYPE		
EXTRANODAL OF MALT	8 (17)	47.1% (23.0, 72.2)
NODAL	20 (32)	62.5% (43.7, 78.9)
SPLENIC	13 (17)	76.5% (50.1, 93.2)
PRIOR BTKI AT ANYTIME		
YES	17 (26)	65.4% (44.3, 82.8)
NO	24 (40)	60.0% (43.3, 75.1)
PRIOR BTKI IN THE LAST LINE		
YES	9 (16)	56.3% (29.9, 80.2)
NO	32 (50)	64.0% (49.2, 77.1)
PRIOR BTKI		
IN THE LAST LINE	9 (16)	56.3% (29.9, 80.2)
NO BTKI	24 (40)	60.0% (43.3, 75.1)



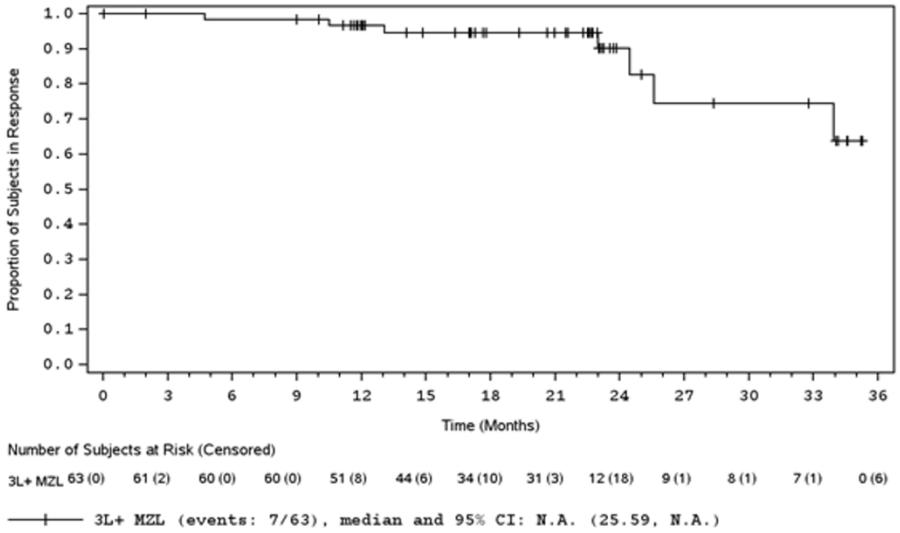
Two-sided 95% CI based on exact Clopper-Pearson method.

CRR difference is not computed for subsets with < 5 subjects per analysis group.

Per the modified GELF criteria, bulky disease is defined as any mass > 7 cm, or 3 or more masses (each > 3 cm) at screening based on Investigator assessment.

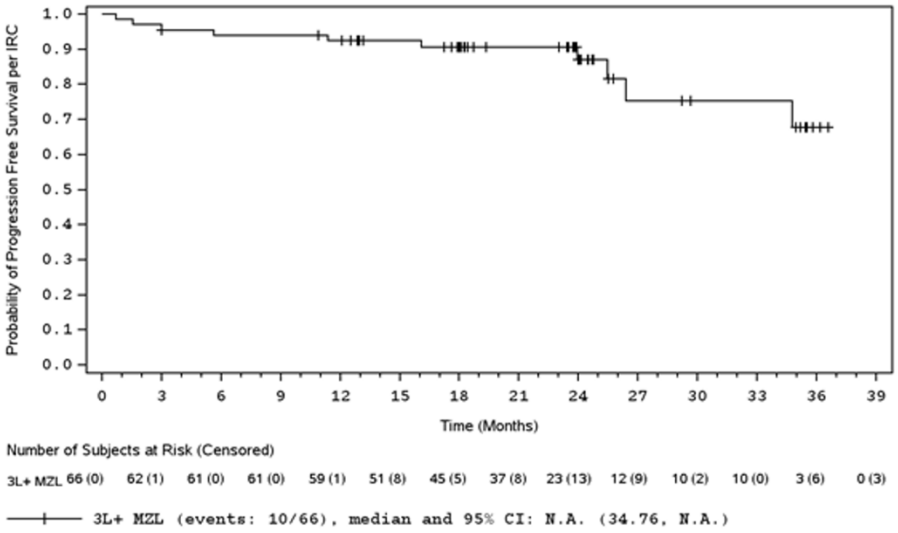
Source: ADSL, ADCORE, ADSUB, ADRS

Figure 4: Applicant - KM Plot of DOR per IRC using FDA Censoring Rules - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL Subjects who Achieved CR or PR - Study FOL-001



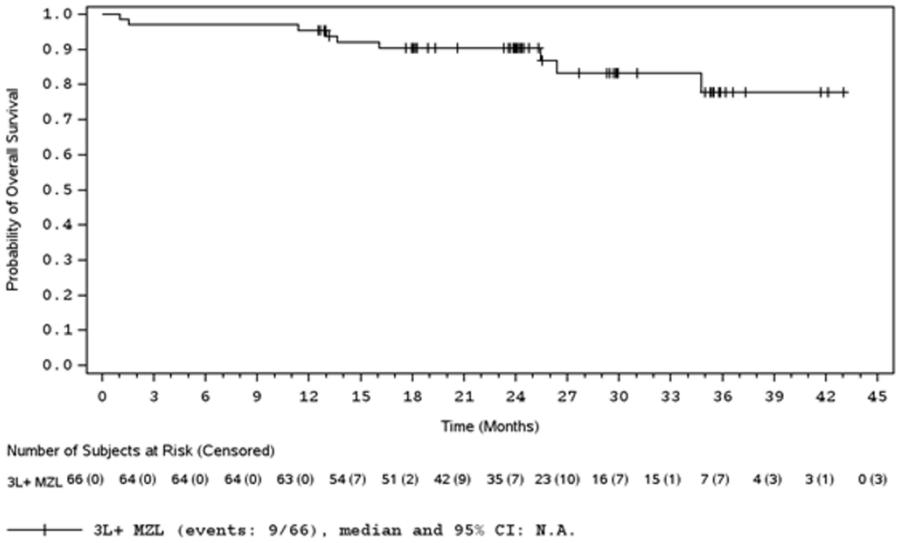
Symbols represent censored observations.
Source: ADSL, ADCORE, ADTTE

Figure 5: Applicant - KM Plot of PFS per IRC using FDA Censoring Rules - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL Subjects - Study FOL-001



Symbols represent censored observations.
Source: ADSL, ADCORE, ADTTE, ADRS

Figure 6: Applicant - KM Plot of OS - Liso-cel-treated Efficacy Analysis Set - 3L+ MZL Subjects - Study FOL-001



Symbols represent censored observations.

Source: ADSL, ADCORE, ADTTE, ADRS

The Applicant's Position:

The key secondary endpoint of CRR per IRC in 3L+ MZL Liso-cel-treated Efficacy Analysis Set was 62.1% (95% CI: 49.3, 73.8) (Table 14). The sensitivity analysis of CRR per Investigator assessment showed a numerically lower CRR (47% [95% CI: 34.6, 59.7]). The numerical difference between the CRR per IRC and per Investigator could be explained by variations in radiographic lesion identification as well as variability in inter-observer response classification, commonly observed in clinical image interpretation for CT-based assessments.[26,27] The CRR per IRC in the Leukapheresed (ITT) Analysis Set was consistent with that in the Liso-cel-treated Efficacy Analysis Set (Table 14).

A high CRR was observed in all subgroups in the Liso-cel-treated Efficacy Analysis Set (Figure 3). CRR was generally consistent across all subgroups although small numerical differences were observed across some subgroups (eg, LDH prior to LDC or MZL subtypes). However, meaningful conclusions could not be drawn due to the imbalance of sample sizes within some subgroups, as well as wide and overlapping CIs.

With a median follow-up for DOR of 21.59 months (95% CI: 17.28, 22.77) and PFS of 23.79 months (95% CI: 19.35, 24.08), respectively, the median DOR and median PFS were not reached (95% CI: 25.59 months, NA) and not reached (95% CI: 34.76 months, NA), respectively (Table 14, Figure 4 and Figure 5). The ORR and CRR per IRC were 95.5% (95% CI: 87.3, 99.1) and 62.1% (95% CI: 49.3, 73.8), respectively, notably higher than the ORR and CRR observed with currently approved treatments in R/R MZL (approximately 65% to 70% and approximately 25% to 40% respectively).[13,14,15,28]

The probability of continued response after initial response was observed to be high at 12 months (96.7%), 18 months (94.6%), and 24 months (90.1%). PFS rates were

observed to be high at 12 months (92.3%), 18 months (90.5%), and 24 months (87.1%) (Table 14).

Sensitivity analyses of DOR and PFS in Leukapheresed (ITT) Analysis Set, using FDA censoring rules showed consistency with IRC-assessed DOR and PFS in the Liso-cel-treated Efficacy Analysis Set.

Overall, DOR and PFS were consistent across all subgroups in the Liso-cel-treated Efficacy Analysis Set. Small numerical differences were noted in some subgroups (eg, LDH prior to LDC, MZL subtypes, or GCSF use). However, meaningful conclusions could not be drawn due to the imbalance of sample sizes within some subgroups, as well as wide and overlapping CIs (ADTTE, ADSUB).

The median OS was not reached (range: 1.1, 43.0+ months) and OS rates were observed to be high at 12 months (95.5%) and both 18 and 24 months (90.4%) (Table 14 and Figure 6). Sensitivity analysis of OS in Leukapheresed (ITT) Analysis Set showed consistency with IRC-assessed OS (median OS not reached [range: 0.8, 44.2+] months; Table 14).

The efficacy results suggest a potential for deep and durable responses in this high-risk 3L+ MZL population with high unmet medical need.

The FDA's Assessment:

Table 28 summarizes the CRR and PR rate in 3L+ R/R MZL patients treated with Liso-cel in Study FOL-001 using IRC assessments of response. The CR rate of 62.1% in the primary efficacy population is higher than that of any available therapy in relapsed or refractory MZL. On subgroup analysis, however, the FDA notes the lower CR rate of 45% (95% CI: 23.1, 68.5) among 20 subjects between the ages of 65 and 75 as compared to the CR rate in 36 subjects under the age of 65 (CRR 69.4% (95% CI: 51.9, 83.7) and 10 subjects age 75 and above (CRR 70% (95% CI: 34.8, 93.3). Also on subgroup analysis, the FDA notes a lower CRR among 14 patients with bulky disease (CRR 42.9% (95% CI: 17.7, 71.1) and 17 patients with extranodal MZL (CRR 47.1% (95% CI: 23, 72.2). Of note, just 26% of patients enrolled on Study FOL-001 had extranodal MZL, and just 21% of all enrolled patients had bulky disease. The small sample sizes and wide confidence intervals on subgroup analysis limit any meaningful conclusions about differences in efficacy. Finally, the FDA notes the limitations of Study FOL-001 as a single arm study with no comparator arm such that any PFS and OS data generated, i.e. time-to-event endpoints, are not felt to be interpretable by the clinical review team. PFS and OS data do not support an efficacy claim in labeling and will not be considered in the benefit-risk assessment.

Table 28 28: FDA - Response Rates in Subjects with R/R MZL Treated with Liso-cel in Study FOL-001

Response rate	Primary Efficacy Population n= 66	All Leukapheresed Patients n=77
Overall Response Rate, n (%)	95.5	84.4
[95% CI]	[87.3, 99.1]	[74.4, 91.7]
Complete Response Rate	62.1	55.8
[95% CI]	[49.3, 73.8]	[44.1, 67.2]
Partial Response Rate	33.3	28.6
[95% CI]	[22.2, 46.0]	[18.8, 40.0]
Source: FDA Analysis of ADRS data- JCAR-FOL-001 and FDA statistical reviewer's memo		

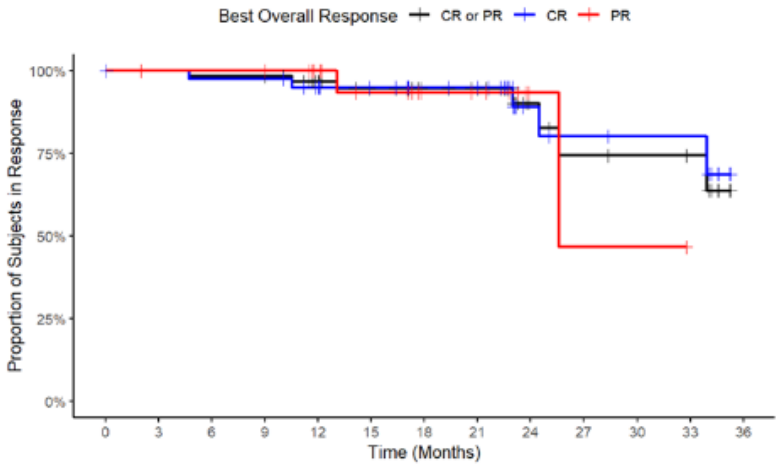
Table 29 summarizes the DOR data among 3L+ MZL patients treated with liso-cel in Study FOL-001. The median DOR was not reached on Study FOL-001 (95% CI: 25.59, NR) after a median followup of 21.59 months. DOR data describing the primary efficacy analysis population which required subjects to have at least nine months of followup after their first objective disease response will be included in the label. Of note, the median DOR was not reached among patients with relapsed or refractory MZL treated on the MAGNIFY study with 12 cycles of lenalidomide and rituximab. The median followup on MAGNIFY, however, was just 11.5 months [95% CI: 8, 18.9). The median DOR was not able to be estimated on the 2 single arm studies that supported the approval of zanubrutinib.

Table 29. FDA - Duration of Response in Patients with Relapsed or Refractory MZL

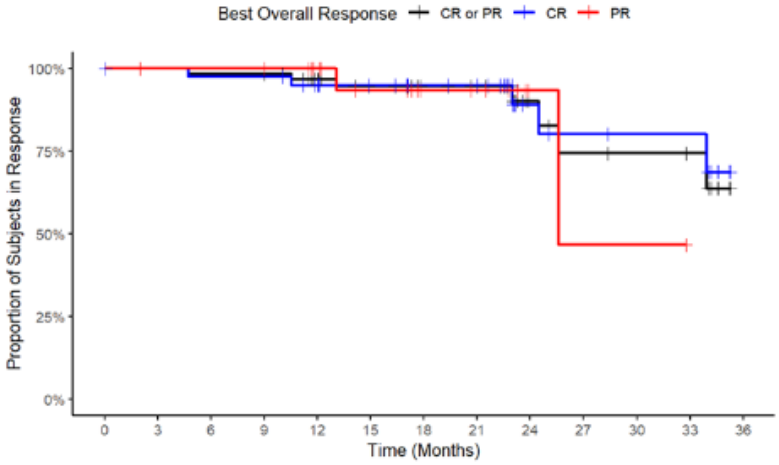
	BREYANZI Treated N = 66
Number of Responders	**63**
DOR (months)	
Median [95% CI][c]	NR [25.59, NR]
Range	0.0+, 35.3+
Rate at 12 months, (%) [95% CI][d]	96.7 (87.3, 99.2)
Rate at 24 months, (%) [95% CI][d]	90.1 (73.1, 96.6)
DOR if best response is CR (months)	**N=41**
Median [95% CI][c]	NR [24.48, NR]
Range	0.0+, 35.3+
Rate at 12 months, (%) [95% CI][d]	94.9 (81.2, 98.7)
Rate(at 24 months, (%) [95% CI][d]	89.0 (66.6, 96.7)
DOR if best response is PR (months)	**N=22**
Median [95% CI][c]	25.59 [25.59, NR]
Range	2.0+, 32.8+
Rate at 12 months, (%) [95% CI][d]	100 (100.0, 100.0)
Rate at 24 months, (%) [95% CI][d]	93.3 (61.3, 99.0)
Median follow up for DOR [95% CI]	21.59 months (17.28, 22.77)

Source: FDA analysis of ADTTE dataset -JCAR-FOL-001 MZL Cohort, and Statistical reviewer memo
DOR= duration of response; CI=confidence interval; CR=complete response; PR=partial response; NR=not reached.
+Indicates a censored value.
[d] KM estimate of probability of continued response at the specified month

Figure 1: Kaplan-Meier Plot of Duration of Response in the Liso-cel Treated Efficacy Analysis Set



(Source: FDA reviewer's summary)



(Source: FDA reviewer's summary)

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 the Applicant's position.

Durability of Response

The Applicant's Position:
Durability of response was demonstrated by DOR, PFS, and OS (Table 14). Study FOL-001 is ongoing to follow-up on long-term efficacy and safety.

The FDA's Assessment:
FDA analysis of DOR is presented in Table 29.

Persistence of Effect

The Applicant's Position:
With a median follow-up of 24.08 (min, max: 1.1, 43.0) months, Study FOL-001 MZL Cohort demonstrated clinical benefit of liso-cel in subjects with 3L+ MZL. Durability of response was demonstrated by DOR, PFS, and OS (Table 14).

In the 3L+ MZL Liso-cel-treated Efficacy Analysis Set, both ORR and CRR were high (95.5% and 62.1%, respectively). With a median follow-up of 21.59 months for DOR and 23.79 months for PFS, the median DOR and median PFS were not reached (95% CI: 25.59 months, NA) and not reached (95% CI: 34.76 months, NA), respectively. DOR rates were observed to be high at 12 months (96.7%), and 18 months (94.6%). PFS rates were observed to be high at 12 months (92.3%) and 18 months (90.5%) (Table 14). The median OS was not reached (95% CI: 1.1, 43.0+ months) and OS rates were observed to be high at 12 months (95.5%) and 18 months (90.4%).

In addition, in the PK Analysis Set, persistence of liso-cel transgene was observed up to Month 42 (Day 1275) in 3L+ MZL subjects.

B-cell aplasia (ie, CD19+ B-cells < 3% of peripheral blood lymphocytes) was observed in 71.2% of subjects at baseline in the 3L+ MZL Cohort, increased to 90.8% of subjects by Day 8, and was maintained in 90.3% of subjects through Day 90. B-cell aplasia continued to be observed in 68.4% of subjects who reached Month 24 (Day 730).

The FDA's Assessment:
Responses per IRC (i.e .CR or PR) were achieved in 63 out of 66 subjects, with the probability of remaining in response at 12 months being 96.7% (95% CI: 87.3, 99.2) and at 24 months 90.1% (95% CI: 73.1, 96.6). 41 patients achieved a BOR of CR, and the estimated probability of remaining in CR at 12 months was 94.9% (95% CI: 87.3, 99.2).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
The PRO Analysis Set (N = 61) consisted of 60 (98.4%), 61 (100.0%), and 60 (98.4%) subjects for the EORTC QLQ-C30 questionnaire, FACT-LymS questionnaire, and EQ-5D-5L Utility Index and VAS, of the Liso-cel-treated Analysis Set, respectively. The

completion rate for all PRO questionnaires was >95% at baseline and remained >70% through Day 545 (Month 18).

EORTC QLQ-C30 - Mean Change from Baseline

After an initial transient deterioration, liso-cel consistently demonstrated improvements over time in evaluations of mean change from baseline on most pre-selected domains of interest on EORTC QLQ-C30 in 3L+ MZL subjects (ADSL, ADCORE, ADQS).

GHS/QoL, role functioning, and pain worsened between Day 1 to Day 15 before demonstrating improvement between Day 15 to Day 60 and remaining consistent thereafter. Physical functioning and fatigue also worsened between Day 1 to Day 15 before demonstrating improvement between Day 15 to Day 90 and remaining consistent thereafter. No clinically meaningful changes from baseline were observed in cognitive functioning (ADSL, ADCORE, ADQS). The mean changes exceeded the contemporary threshold for clinically meaningful improvement at some visits. For the primary domains of the EORTC QLQ-C30, the proportion of subjects experiencing clinically meaningful improvement or no change was higher than that of clinically meaningful worsening, across all time points.

FACT-LymS

The 3L+ MZL subjects treated with liso-cel showed improvement from baseline in lymphoma-specific symptoms as assessed by FACT-LymS as early as Day 15, reaching clinically meaningful improvement by Day 60 and remaining consistent thereafter. The proportion of subjects experiencing clinically meaningful improvement or no change on FACT-LymS was higher than that of clinically meaningful worsening across all timepoints (ADSL, ADCORE, ADQS).

EQ-5D-5L Summary Index - Mean Change from Baseline

The 3L+ MZL subjects treated with liso-cel showed improvement from baseline in the EQ-5D-5L summary index between Day 1 and Day 60 and remained stable until Day 365 following which a downward trend was observed. The improvement or deterioration did not reach the clinically meaningful threshold (ADSL, ADCORE, ADQS).

EQ-5D-VAS Summary Index - Mean Change from Baseline

The 3L+ MZL subjects treated with liso-cel showed improvement in the EQ-5D-5L VAS between Day 1 to Day 90 and remained consistent thereafter. The improvements did not reach clinically meaningful improvement threshold (ADSL, ADCORE, ADQS).

Hospital Resource Utilization

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

In the 54 (80.6%) 3L+ MZL subjects who received liso-cel and who were monitored as inpatients, the most common reason for hospitalization during liso-cel infusion was 'other' (90.6%), with 'prophylaxis for CAR T cell administration' reported as the most frequent reason. The median duration of hospitalization from time of liso-cel administration was 14 (range, 4 to 42) days. No subjects were admitted to the ICU during liso-cel administration

(ADSL, ADCORE, ADHO, ADHOS).

In the 13 (19.4%) subjects who were monitored as outpatients, 11 (84.6%) subjects were hospitalized after liso-cel administration due to an AE. The median time from liso-cel administration to first hospitalization was 5 days (range, 2 to 159) with a median duration of hospitalization of 7 (range: 2, 10) days. No subjects were admitted to the ICU during or after liso-cel administration (ADSL, ADCORE, ADHO, ADHOS). No subjects who were monitored in the outpatient setting experienced Grade ≥ 3 CRS or iiNT.

The FDA's Assessment:
Patient-reported outcome data is considered descriptive outside of a randomized controlled trial. 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 FOL-001 forms the sole basis for the efficacy claim of liso-cel in the treatment of relapsed and refractory MZL. 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 applicable

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:
The sBLA for liso-cel in the treatment of adult patients with 3L+ MZL is supported by efficacy results from the single-arm, multicenter, Phase 2, Study FOL-001. As summarized in Section 8.1.2, data from Study FOL-001 MZL Cohort demonstrated clinically meaningful high ORR and CRR after liso-cel treatment in subjects with 3L+ MZL.

The study enrolled MZL subjects that had received at least two prior lines 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 heavily pretreated (≥ 3 prior lines of systemic therapy; 55.2%), POD24

(35.8%), refractory disease (38.8%), and prior autologous stem cell transplantation (16.4%).

Study FOL-001 MZL Cohort evaluated the efficacy of liso-cel, an anti-CD19 CAR T-cell therapy in 66 evaluable subjects with 3L+ MZL. In the 3L+ MZL population (N = 66), liso-cel monotherapy demonstrated substantially higher ORR and CRR in the Liso-cel-treated Efficacy Analysis Set compared to approved treatment options in this patient population.[13,14,15,28] Durability of response was demonstrated by the DOR, PFS, and OS. In sensitivity analysis, efficacy was consistent between the Leukapheresed (ITT) Analysis Set and Liso-cel-treated Efficacy Analysis Set. Liso-cel efficacy was also generally consistent across all subgroups. Together, the efficacy results suggest a potential for deep and durable responses in this high-risk 3L+ MZL population with high unmet medical need.

The FDA's Assessment:
No integrated assessment of efficacy was performed, because the efficacy data derives from a single adequate and well controlled trial: JCAR-FOL-001 Cohort 4.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:
Safety data are provided for 67 Liso-cel-treated Analysis Set subjects with 3L+ MZL enrolled in Cohort 4 of 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 3L+ MZL population (Cohort 4) is also presented side-by-side and pooled with the safety population of 3L+ and 2L LBCL, 3L+ CLL/SLL, 3L+ FL, and 3L+ MCL (Table 22).

The FDA's Assessment:
The Applicant defined a treatment emergent adverse event (TEAE) as any adverse event (AE) that starts from initiation of liso-cel administration through and including 90 days after liso-cel administration. The review team defines adverse drug reactions as any treatment emergent adverse event (TEAE) occurring after the start of liso-cel infusion regardless of the perceived relationship and causality with liso-cel. The Applicant's reporting of AEs by preferred terms may underestimate the incidence of some adverse events. The FDA, therefore, used grouped preferred terms to group adverse events that represent the same disease process. Grouping practices previously implemented in the review of similar products within this class of therapies were applied.

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.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26. AE severity was graded using the National Cancer Institute's Common Terminology for Adverse Events version 5. CRS severity was graded according to the grading scale adapted from Lee (Lee 2014). Analyses were performed using JMP Clinical v.18 (SAS Institute, Inc).

The FDA safety review focused on the following:
1. Primary Safety Population from Study FOL-001: includes 67 MZL patients with 2 or more prior lines of systemic therapies (Cohort 4) treated with conforming liso-cel with the data cutoff date of November 29, 2024.
2. Integrated Safety Population: includes 961 liso-cel treated patients from the studies shown below. The integrated safety dataset is considered supportive only.
   a. Study 017001: 268 large B cell lymphoma and 88 mantle cell lymphoma subjects
   b. Study 017004: 117 chronic lymphocytic leukemia/small lymphocytic lymphoma subjects
   c. Study 017006: 61 large B cell lymphoma subjects
   d. Study 017007: 82 large B cell lymphoma subjects
   e. JCAR017-BCM-001: 82 large B cell lymphoma subjects
   f. JCAR017-BCM-003: 89 large B cell lymphoma subjects
   g. JCARFOL-001: 107 follicular lymphoma subjects and 67 MZL subjects
3. Review of the 90 day safety report submitted by the Applicant on August 6, 2025 with a data cutoff of March 31, 2025.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 30: Applicant - Exposure to LDC - Liso-cel-treated Analysis Set

	3L+ MZL (Cohort 4) N = 67
Fludarabine	
Subjects who Received	
Full Dose of Fludarabine[a] - n (%)	50 (74.6)
Adjusted Dose of Fludarabine[b] - n (%)	16 (23.9)
Not Administered Dose[c] - n (%)	1 (1.5)
Cyclophosphamide	
Subjects who Received	
Full Dose of Cyclophosphamide[a]- n (%)	67 (100.0)
Time From Last Dose of Lymphodepleting Chemotherapy to Liso-cel Infusion (Days)	
Median	4
Min, Max	4, 12

[a] Received full dose, no missing dose.

[b] Received at least one adjusted dose but did not miss a dose.

[c] Missed at least one dose.

Source: ADSL, ADCORE, ADEX, ADEXS

Table 31. Applicant - Liso-cel Exposure - Liso-cel-treated Analysis Set

	3L+ MZL (Cohort 4) N = 67
Liso-cel CD8+ Cells	
Total Number of Liso-cel CD8+ Cell Counts Infused (10^6 Cells)	
Median	50.13
Min, Max	48.4, 51.6
Liso-cel CD4+ Cells	
Total Number of Liso-cel CD4+ Cell Counts Infused (10^6 Cells)	
Median	50.15
Min, Max	48.1, 51.6
Combined Liso-cel Dose	
Total Number of Liso-cel CD4+ And CD8+ Cell Counts Infused (10^6 Cells)	
Median	100.15
Min, Max	97.3, 102.8

Source: ADSL, ADCORE, ADEX, ADEXS

The Applicant's Position:

LDC: The median time from end of LDC to liso-cel infusion (4 days; range, 4 to 12; Table 15). Per protocol, liso-cel infusion was to be administered 2 to 7 days after completion of LDC and any delay in liso-cel infusion after the completion of LDC required discussion with the Medical Monitor. Following discussion with the Medical Monitor, 4 subjects received liso-cel infusion > 7 days after the completion of LDC due to ongoing medical history events and/or adverse events.

Manufacturing: In the Leukapheresed (ITT) Analysis 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: 21 to 44). The median time from leukapheresis to liso-cel infusion was 50.0 days (range: 30 to 121) (ADEX, ADEXS).

Manufacturing failure rate was defined as the number of subjects for whom liso-cel product (conforming at time of release) could not be manufactured divided by the number of subjects who had leukapheresis and manufacturing information available x 100. Manufacturing failure was infrequent (3/76 [3.9%] subjects). No manufacturing attempt was made for 1 subject out of the Leukapheresed (ITT) Set (N = 77) because the subject was no longer eligible for the study shortly after the leukapheresis procedure (ADEX, ADEXS).

Liso-cel treatment: The median liso-cel administered dose (CD4+ and CD8+: 100.15 × 10^6 CAR+ T cells (range: 97.3 × 10^6 to 102.8 × 10^6) Table 16) was consistent with the protocol-specified dose of 100 × 10^6 CAR+ T cells.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Liso-cel doses were administered within the proposed marketing dose of 90 to 110 X 10-6 CAR+ viable T cells. In 67 3L+ MZL

patients included in the FDA's safety analysis, the median dose administered was 100.15 × 10^6 CAR+ T cells (range: 97.3 × 10^6 to 102.8 × 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 = 67) were consistent with the expected characteristics of subjects with R/R MZL. Details are provided in Section 8.1.2.

The FDA's Assessment:
The clinical safety review was based on analysis of data that includes 67 subjects from Cohort 4 of Study FOL-001 treated with a single, conforming dose of liso-cel after receiving lymphodepleting chemotherapy (LDC). The study data cutoff date was November 29, 2024.

Table 32 summarizes the demographics and baseline characteristics of the safety population. Among the 67 patients in the safety population, the median age was 62, 58% were male, the majority of patients were white at 57%, 48% were from the US, and all patients had an ECOG performance status of 0-1. The FDA also notes that the majority of MZL patients enrolling on Study FOL-001 had nodal MZL (48%) despite extranodal MZL being the most frequent MZL subtype. There was limited representation regarding race and ethnicity with 6% Asian, 1.5% Black, and 1.5% Hispanic.

As previously noted in section 8.1, an indication for systemic treatment was not required for relapsed or refractory patients enrolling on Study FOL-001. Cohort 4 was only required to have received at least 2 prior systemic therapies, including at least one line of combination therapy, therapy with an anti-CD20 antibody and an alkylating agent, or relapsed after HSCT. The FDA notes that 14% of enrolled patients had stage 1-2 disease, 64% did not have POD24 disease, 78% did not have bulky tumor, and 77% did not have B symptoms.

Table 32: FDA - Demographics and Baseline Characteristics- Study FOL-001

Demographics	Safety Population n= 67	ITT Population N= 77
Age		
Median	62	64
< 65	37 (55)	39
65-75	20 (30)	26
>75	10 (15)	12
Min, Max	37, 81	37, 81

Sex Male Female	 39 (58) 28 (42)	 47 (61) 30 (39)
Ethnicity Hispanic Not Hispanic Not Reported	 1 (1.5) 45 (67) 21 (31)	 3 (4) 50 (65) 24 (31)
Race Asian Black White Unknown	 4 (6) 1 (1.5) 38 (57) 24 (36)	 4 (5) 2 (3) 43 (56) 28 (36)
Region Europe Japan North America US	 31 (46) 2 (3) 34 (51) 32 (48)	 35 (45) 2 (3) 40 (52) 38 (49)
MZL Subtype Extranodal Nodal Splenic	 17 (25) 32 (48) 18 (27)	 19 (25) 37 (48) 21 (27)
Relapsed or refractory[1] Relapsed Refractory	 41 (61) 26 (39)	 45 (58) 32 (42)
ECOG PS 0 PS 1	 37 (55) 30 (45)	 41 36
Stage 1 2 3 4	 3 (4.4) 7 (10) 8 (12) 49 (73)	 3 (4) 7 (9) 9 (12) 58 (75)
POD24 Yes No NE	 24 (36) 43 (64) 0	 25 (33) 50 (65) 2 (3)
Bone marrow involvement Yes No Not reported	 28 (42) 38 (57) 1 (1.5)	 33 (43) 41 (53) 3 (4)

Gastric Involvement Yes No Not reported	 1 (1.5) 16 (24) 50 (75)	 1 (1) 18 (23) 58 (75)
Bulky Yes No	 15 (22) 52 (78)	 18 (23) 59 (77)
B symptoms No Yes	 52 (77) 15 (22)	 57 (74) 20 (26)
Number of prior systemic therapies[2] Median Min, Max	 3 2, 12	 3 2, 12
Prior Splenectomy for Splenic MZL[3] Yes No	 5 (7.5) 62 (92.5)	 6 (7.8) 71 (92.2)
Prior HSCT Yes No	 11 (16.4) 56 (84)	 11 (14.2) 66 (85.7)

[1]Relapsed or refractory disease was assessed by the investigator. Relapsed lymphoma was defined as relapsed after an initial response of CR or PR to the prior therapy. Refractory lymphoma was defined as a best response of SD or PD after prior therapy.
[2]Antibiotics for extranodal MZL were not considered a prior line of therapy.
[3]Splenectomy for splenic MZL was considered a prior line of therapy.

Adequacy of the safety database:

The Applicant's Position:
The number of subjects 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 3L+ MZL population.

With a sample size of 67 subjects and a median study follow-up of 24.08 months, liso-cel exposure in 3L+ MZL subjects was similar to that in the pooled safety population. 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:
Safety data from 67 relapsed or refractory MZL patients treated in the 3L setting provides adequate data to inform the safety of the intended population. Data provided

from 961 liso-cel treated patients in the integrated safety dataset provides additional supportive information.

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 events of clinical interest 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:
The FDA agrees with the Applicant. The 90-day safety update was provided on August 5, 2025.

Categorization of Adverse Event

The Applicant's Position:
All AEs were coded using MedDRA Version 26.0. 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 (2014)[25], 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. iiNT was captured using the PT "Neurotoxicity" and graded (NCI CTCAE version 5.0) on the basis of the highest individual symptom grade. TLS was graded according to the Cairo-Bishop criteria.[29]

AEs were analyzed with a focus on TEAEs, defined as any AE that began from the start of liso-cel infusion through and including 90 days after infusion. 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.

An AESI is an AE of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the Investigator to the Applicant. AESIs for liso-cel included: CRS, iiNT, MAS, TLS, infusion-

related reactions, Grade ≥ 3 infections, hypogammaglobulinemia, autoimmune disorders, SPM, and prolonged cytopenias (defined as Grade ≥ 3 laboratory results of decreased hemoglobin, decreased neutrophil count, or decreased platelet count at the Study Day 29 visit [29 ± 2 days after liso-cel administration]). Time to onset and resolution of the first CRS or iiNT were summarized. Multiple events in an AESI category occurring close to each other (eg, if the start date of one CRS event is within 7 days of the end date of an earlier CRS event) 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:
The FDA notes that the Applicant defined iiNT, or investigator-identified neurotoxicity, as "CAR-T related Investigator-identified NT events". The individual signs and symptoms of the iiNT events were captured separately on the "Neurotoxicity" Details CRF and are described in section 8.2.4. The review team, however, defines adverse drug reactions as any treatment emergent adverse event (TEAE) occurring after the start of liso-cel infusion regardless of the perceived relationship and causality with liso-cel. In the Applicant's response to an FDA Information Request dated December 2, 2025, the Sponsor clarified the inclusion of a separate category of Neurological Toxicity in the ADAE dataset defined as adverse events belonging to the Nervous System Disorders or Psychiatric System Disorders SOC, regardless of investigator assessment of relatedness. The FDA notes that the analysis of time to resolution of an AESI excluded subjects with unresolved events.

Routine Clinical Tests

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

The FDA's Assessment:
The FDA agrees with the Applicant.

8.2.4. Safety Results

Table 3332: Applicant - Overall Summary of Safety in Study FOL-001

Safety Parameter	3L+ MZL (Cohort 4), n (%)
Leukapheresed (ITT) Analysis Set	**N = 77**
Deaths[a]	16 (20.8)
Primary Cause of Death	
PD	6 (7.8)
AE (NOS)	1 (1.3)
Cardiac Event	2 (2.6)
Other	5 (6.5)
New Malignancy or Complication from New Malignancy	2 (2.6)
Liso-cel-treated Analysis Set	**N = 67**
Subjects with any TEAE	67 (100.0)
Grade ≥ 3	59 (88.1)
Grade 5	2 (3.0)
Serious TEAE	26 (38.8)
Liso-cel-related TEAE	63 (94.0)
Liso-cel-related Grade ≥ 3	44 (65.7)
Liso-cel-related Grade 5	2 (3.0)
Liso-cel-related serious TEAE	20 (29.9)
LDC-related	54 (80.6)
Subjects with any AESI	55 (82.1)
CRS[b]	51 (76.1)
Median Time to First Onset of CRS[c], days (range)	4 (1, 29)
Median Time to Resolution of First CRS[d], days (range)	4 (1, 13)
Maximum Toxicity Grade	
Grade 1	31(46.3)
Grade 2	17 (25.4)
Grade 3	3 (4.5)
iiNT[e]	22 (32.8)
Median Time to First Onset of iiNT[c], days (range)	8.5 (2, 36)
Median Time to Resolution of First iiNT[f], days (range)	8.0 (1, 90)
Maximum Toxicity Grade	
Grade 1	10 (14.9)
Grade 2	9 (13.4)
Grade 3	3 (4.5)
IRR	0
MAS	3 (4.5)
TLS	1 (1.5)
Hypogammaglobulinemia[g,k]	3 (4.5)
Grade ≥ 3 infections	6 (9.0)
SPM[g,h]	8 (11.9)
Autoimmune disorders[g,i]	0
Prolonged cytopenia[j]	28 (41.8)

[a] Deaths from GC-LTFU-001 (LTFU) were included.

[b] CRS was graded based on Lee criteria (2014).[25]

[c] Time to onset was calculated from liso-cel infusion to the first onset of the event.

[d] Any CRS events that stop/start within 7 days (start date-stop date ≤ 7) were considered in a single episode. Time to resolution of CRS was defined when the last CRS event of the first episode ended. Subjects with an unresolved event in the episode were excluded.

[e] iiNT was captured using the PT "Neurotoxicity" and graded (CTCAE version 5.0) on the basis of the highest individual symptom grade.

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

[g] Hypogammaglobulinemia, SPM and Autoimmune disorder events were collected during and after the treatment-emergent period.

[h] SPM based on findings from SMQ searches for "Premalignant Disorders" and "Malignancies" and subsequent
medical review by an internal adjudication panel. The adjudication of SPMs consisted of reviewing the preferred
terms detected during the SMQ search and selecting AEs clinically appropriate for inclusion as malignancies.

[i] Autoimmune Disorders based on finding from the search for "Autoimmune Disorders" high-level group term plus
PTs: temporal arteritis, granulomatosis with polyangiitis, vasculitis, Behcet's syndrome, Basedow's disease, erythema nodosum, Crohn's disease, Felty's syndrome, rheumatic brain disease and subsequent medical review for
internal adjudication.

[j] Prolonged Cytopenia is defined as Grade ≥ 3 laboratory results of decreased hemoglobin, neutrophil count, or platelet count at the Day 29 (±2 days) visit.

[k] Hypogammaglobulinemia includes post-liso-cel AEs coded to the following MedDRA PTs: blood immunoglobulin A decreased, blood immunoglobulin D decreased, blood immunoglobulin E decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, immunoglobulins decreased, selective IgA immunodeficiency, selective IgG subclass deficiency and selective IgM immunodeficiency.

A liso-cel TEAE was defined as any AE that occurred from start of liso-cel infusion and up to 90 days after liso-cel infusion. Any AE occurring after the initiation of another anticancer treatment was not considered a TEAE. Related AEs were those for which the Investigator selected 'Related' to liso-cel or LDC on the AE CRF.

Source: ADSL, ADCORE, ADAE, ADCPT, ADAETTE, ADAES

Deaths

Data:

Table 3433: Applicant -Summary of Deaths and Causes - Leukapheresed (ITT) Analysis Set

	3L+ MZL (Cohort 4; N = 77); n (%)
Overall Number of Deaths	16 (20.8)
Cause of Death	
PD	6 (7.8)
AE (NOS)	1 (1.3)
Cardiac Event[c,f]	2 (2.6)
Other Cause[a,d,g]	5 (6.5)

Table 3433: Applicant -Summary of Deaths and Causes - Leukapheresed (ITT) Analysis Set

	3L+ MZL (Cohort 4; N = 77); n (%)
New Malignancy or Complication from New Malignancy	2 (2.6)
Deaths	
Between Leukapheresis and LDC Start[b]	6 (7.8)
Cause of Death	
PD	4 (5.2)
Cardiac Event[c]	1 (1.3)
Other Cause[d]	1 (1.3)
Between LDC And Infusion[e]	0
Infusion, Day 1- 30	0
Infusion, Day 31- 90	2 (2.6)
Cause of Death	
AE (Not Otherwise Specified)	1 (1.3)
New Malignancy or Complication from New Malignancy	1 (1.3)
From Infusion, ≥ Day 91[e]	8 (10.4)
Cause of Death	
PD	2 (2.6)
Cardiac Event[f]	1 (1.3)
Other Cause[a,g]	4 (5.2)
New Malignancy or Complication from New Malignancy	1 (1.3)

[a] Includes 1 subject that received NCP.
[b] If LDC start date is not available, death is included in this section.
[c] Death from 'Cardiac Event' included: cardiovascular complication (1 subject).
[d] Death from 'Other Cause' included: suicide (1 subject).
[e] If LDC start date is available and infusion date is not available, death is included in this section.
[f] Death from 'Cardiac Event' included: sudden cardiac death (1 subject).
[g] Death from 'Other Cause' included: pneumonia (2 subjects), COVID-19 (2 subjects)
Source: ADSL, ADCORE

The Applicant's Position:

In the Leukapheresed (ITT) Analysis Set, a total of 16 (20.8%) subjects died during the study. 6 deaths occurred between leukapheresis and start of LDC and 10 deaths occurred after infusion. None of the subjects died between LDC and before liso-cel infusion or within 30 days after liso-cel infusion. Two (2.6%) subjects died between 31-90 days after liso-cel infusion (one each due to AE and new malignancy or complication from new malignancy, both of which were assessed as suspected to be related to liso-cel by the investigator), and 8 (10.4%) subjects died after the 90-day post-infusion period (including 1 subject who received NCP) (mainly due to Other causes and PD) (Table 18).
Two (3.0%) subjects experienced a TEAE that led to death. These TEAEs were neutropenic sepsis and T-cell lymphoma (1 [1.5%] subjects each), which were assessed as suspected to be related to liso-cel treatment by the investigator (ADSL, ADCORE, ADAE).

The FDA's Assessment:

The FDA notes that there were a total of 16 deaths in the ITT population on Study FOL-001 by the November 29, 2024 data cutoff date as shown in Table 36 below. The FDA agrees that two subjects experienced a TEAE due to neutropenic sepsis and a T cell lymphoma; however, the patient who died of neutropenic sepsis had ongoing concurrent neurotoxicity as described below which may have contributed to his death. Five total deaths on Study FOL-001 occurred in the setting of disease progression including a patient who was a screening failure (USUBJID (b) (6)). Additional causes of death as described below included 1 AML, 3 infection-related deaths while on other therapies (i.e. 2 pneumonias and 1 sepsis), 2 cardiac deaths, 2 COVID-related deaths, 1 respiratory failure, and 1 suicide.

Table 3435: FDA - Deaths on Study FOL-001

USUBJID	Liso-cel Treated	Clinical history	Cause of Death
(b) (6)	Yes	71 y/o man with stage IV splenic MZL	Death from Adverse Event (neutropenic sepsis) on day + 47
	Yes	52 y/o woman with stage IV nodal MZL	Death from Adverse Event (New Malignancy: T-cell lymphoma) on day + 32
	Yes	57 y/o man with stage IV nodal MZL	Death from New Malignancy (AML) on day +490
	Yes	55 y/o woman with stage IV splenic MZL	Pneumonia in setting of MDS related treatment on day +775
	Yes	67 y/o woman with stage IV nodal MZL	Klebsiella PNA while on JAK2 inhibitor on day + 1058
	Yes	62 y/o man with stage IV extranodal MZL	Sepsis during new antilymphoma therapy on day +416
	Yes	76 y/o woman with stage IV nodal MZL	Respiratory failure in setting of PNA, pleural effusion, and NHL Progression on Day +396
	Yes	81 y/o man with stage IV nodal MZL	Death from cardiac event (sudden cardiac death) on day 803.
	No	68 y/o man with stage IV nodal MZL	Death from Cardiac Event (cardiovascular complications)
	No*	67 y/o man with stage IV nodal MZL	COVID-19 on day + 358.
	Yes	72 y/o woman with stage IV splenic MZL	SARS-COV2 infection on day +346
	No	71 y/o man with stage IV nodal MZL	NHL Progression Between Leukapheresis

(b) (6)			and LDC
	No	81 y/o man with stage IV splenic MZL	NHL Progression Between Leukapheresis and LDC
	No	68 y/o man with stage IV extranodal MZL	NHL Progression Between Leukapheresis and LDC
	No	60 y/o woman with stage IV nodal MZL	NHL Progression Between Leukapheresis and LDC
	No	81 y/o woman	NHL Progression During Screening
	No	Stage IV extranodal MZL	Suicide

*** nonconforming product**

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

1. SUBJID: (b) (6)

71 y/o man with stage 4 splenic MZL initially diagnosed in 2007 who died on day 47 due to neutropenic sepsis with ongoing events of delirium, confusion, restlessness, and subdural hygroma. The patient developed grade 3 peripheral neuropathy complicated by a fall on day 16, grade 3 confusional state on day 17, and grade 1 aphasia on day 18. MRI brain showed a 1.5 cm left frontal meningioma. Patient received intravenous decadron (in addition to risperidone and quetiapine) for neurotoxicity which waxed and waned between a grade 2 confusional state and grade 3 confusional state before resolving on day 36, the day of hospital discharge. The patient was readmitted on day 42 with grade 3 neutropenic sepsis and grade 3 confusional state. "The subject did not respond to communication but was awake, further described as grade 4 ICANS considered by the investigator to be due to neutropenic sepsis". The patient developed grade 3 restlessness on day 43 which is the same day blood cultures became positive for Klebsiella pneumoniae and E.coli for which he received broad spectrum antibiotics. The patient was subsequently diagnosed with a grade 1 subdural hygroma on day 46 in addition to receiving a diagnosis of diabetes insipidus before his death on day 47 with ongoing events of delirium, confusion, restlessness, and subdural hygroma as previously described.

Reviewer's assessment: The grade 5 event of neutropenic sepsis is hard to dissociate from the concurrent neurologic symptoms of delirium, confusion, and restlessness and a patient who "did not respond to communication... further described as grade 4 ICANS" by the investigator. The clinical review team believes Klebsiella and E.Coli bacteremia contributed to the patient's death, but suspects there was a concurrent neurologic toxicity that contributed to the patient's death given onset of grade 3 confusional state on day 17 that preceded the onset of neutropenic sepsis on day 43.

2. SUBJID: (b) (6)

50 y/o woman with stage 4 nodal MZL diagnosed in 2015, s/p multiple treatments

including ASCT (b) (6) with progressive disease (b) (6), s/p bridging RCHOP 7/2023 and zanubrutinib 9/2023-10/2023, course complicated by neutropenic colitis, s/p lymphodepleting chemotherapy 10/2023 and liso-cel administration (b) (6), died from a T cell lymphoma on day 32. The patient presented with two new splenic lesions on CT on day 22 retrospectively diagnosed as a grade 4 T-cell lymphoma based on autopsy findings. Followup PET on D29 showed uptake in the bone marrow, spleen, and liver. The histopathology report revealed a diffuse infiltration within the mesenteric and aortic lymph nodes, resulting in effacement of the lymph node architecture and extracapsular extension. Necrosis was evident. The cells had marked atypia with spindle cell morphology and hyperchromatic nuclei along with dense eosinophilic cytoplasm. There were also atypical cells identified in liver sections. Immunohistochemistry on a lymph node and liver block showed diffuse positivity for CD45. Interpretation of stains was challenging due to tissue autolysis, but a proportion of cells on a lymph node and liver block were positive for CD4, CD3, CD5, CD30, and bF1. CD2 and CD8 positive T cells were identified. The investigator concluded a probable de-novo development of a T cell lymphoma extensively involving the liver. DNA-based droplet digital PCR detected 33, 927 copies/microgram in the liver and 12, 377 copies/microgram in the aortic lymph node versus 51, 6000 copies/microgram in the peripheral blood. Insertion site analysis conducted on the liver and aortic lymph node samples revealed that the CAR+ cell population was polyclonal. Among the top 10 integration sites reported in the 7 samples where ISA was conducted (2 tumor tissues and 5 blood samples), there were no common integration sites identified among the samples.

Reviewer's Assessment: Given the onset of symptoms just 22 days after infusion of liso-cel, despite the negative integration site analysis, the clinical review team attributes the onset of T-cell lymphoma to treatment with liso-cel.

3. SUBJID: (b) (6)
57 y/o man with stage 4 nodal MZL initially diagnosed in 2016, s/p RCHOP, BR, carboplatin/cytarabine/rituximab/decadron followed by ASCT and gemcitabine and oxaliplatin, with day 473 diagnosis of AML to which he succumbed on day 490 490. Post-CAR-T infusion course was otherwise remarkable for grade 3 prolonged thrombocytopenia diagnosed on day 23 which improved to grade 2 by day 94. Thrombocytopenia persisted through day 360 (platelet count 55000). No autopsy was performed.

Reviewer's assessment: The clinical review team attributes development of AML to treatment related AML in setting of patient's prior exposure to high dose chemotherapy in the setting of her autologous stem cell transplant.

4. SUBJID (b) (6)
55 y/o woman with stage 4 splenic MZL diagnosed October 2017, s/p multiple therapies

including bridging bendamustine and obinutuzumab November 2021, with day 552 diagnosis of grade 4 myelodysplastic syndrome with D775 death due to pneumonia. Day 542 bone marrow biopsy was notable for megakaryocytic dysplasia and cytogenetics with 7Q31 deletion and indeterminate RNAscope in-situ hybridization for the transgene. Patient received decitabine and cedazuridine for her MDS. Bone marrow biopsy for lymphoma was negative on day 600.

Reviewer's assessment: The clinical review team attributes development of MDS to treatment related MDS in the context of patient's prior exposure to chemotherapy and accepts patient's death in the context of a pneumonia which occurred while receiving therapy for MDS.

5. SUBJID (b) (6)
67 y/o woman with stage IV nodal MZL, who died on day 1058 of Klebsiella pneumonia while on a JAK inhibitor; however, the context of an evolving granulomatous process that occurred following the administration of liso-cel is important. On day 177, the patient had a skin biopsy consistent with a grade 2 granuloma. On day 183, the patient developed dermatitis on her back and arms, new joint stiffness, scleritis, and abnormal LFTs. Symptoms were refractory to topical steroids, sulfasalazine, and hydroxychloroquine. On day 357, the patient developed a disseminated papular rash on her trunk and extremities with some reported improvement on hydroxychloroquine. Day 414 skin biopsy confirmed the presence of a granulomatous dermatitis. A skin biopsy on day 457 was sent for EGFR staining to assess for a relationship to CAR cells and was negative. Interstitial granulomatous dermatitis was diagnosed day 487 in the setting of symptoms of polyarthralgia and scleritis for which the patient received sulfasalazine and prednisolone eye drops. LFT abnormalities were noted on day 520, and tofacitinib was initiated on day 723 with improvements in the skin, joints, eyes, and ultimately LFTs. When tofacitinib was discontinued in January 2024 for thrombocytopenia, patient's skin, eye, and joint symptoms progressed and new lung nodules developed in February 2024. Widespread centrilobular nodules were noted on day 919 for which Upadacitinib was started followed by a diagnosis of grade 2 squamous cell carcinoma on day 1024. Patient died from Klebsiella pneumonia on day 1058 in the setting of JAK inhibitor use and in the setting of an underlying autoimmune process.

Reviewer's assessment: Although the patient died from a Klebsiella pneumonia that occurred while the patient was on a JAK inhibitor, the clinical team feels the patient's underlying autoimmune disorder that evolved following liso-cel infusion is an important contributor to the patient's immune dysfunction alongside the immunosuppression generated by the JAK inhibitior.

6. SUBJID (b) (6) :
62 y/o man with stage 4 extranodal MZL, who developed sepsis on day 416 following

administration of NALT.

Reviewer's assessment: The clinical team agrees that sepsis occurred in the setting of immunosuppression precipitated by a new treatment for the patient's lymphoma.

7. SUBJID (b) (6)
76 y/o woman with stage 4 nodal MZL who progressed on liso-cel on day 172 and subsequently died from respiratory failure on day 396 while on NALT. Patient's course was notable for day 24 tremors, day 24 grade 2 bacterial enterocolitis which resolved by day 48 following treatment with doxycycline, and day 26 LFT abnormalities which resolved by day 81. The patient's disease progressed on day 172 after which she received NALT. The patient was admitted on day 392 with colitis and died on day 396 with respiratory failure presumed due to pneumonia, pleural effusions, and lymphoma progression. No autopsy was performed.

Reviewer's assessment: The clinical team acknowledges that pneumonia, pleural effusions, and lymphoma progression occurred after NALT administered beyond day 172. However, the team questions the etiology of the recurrent symptom of colitis which initially presented on day 24 and resolved on day 48 and recurred again on day 392 followed by the patient's death on day 396. The patient had no PMH significant for inflammatory bowel disease.

8. SUBJID (b) (6) :
81 y/o man with stage IV nodal MZL with sudden cardiac death on day 803. No autopsy was performed.

Reviewer's assessment: The clinical team agrees with the Applicant's assessment.

9. SUBJID (b) (6)
68 y/o man with stage IV nodal MZL who failed to meet treatment criteria and never received liso-cel and died from cardiovascular complications.

Reviewer's assessment: The clinical team agrees with the Applicant's assessment.

10. SUBJID (b) (6)
67 y/o man with stage 4 nodal MZL, vaccinated against COVID-19 prior to administration of liso-cel (b) (6)), with stable disease determined by IRC on day 270 (b) (6)), s/p COVID booster on day 272 (b) (6) , and death from COVID-19 on day 358 (b) (6) .

Reviewer's assessment: The clinical team agrees with the Applicant's assessment.

11. SUBJID (b) (6)
72 y/o woman with stage IV splenic zone MZL with CR on D270 followed by death on day 346 (b) (6) due to COVID despite COVID vaccinations on (b) (6) .

Reviewer's assessment: The clinical team agrees with the Applicant's assessment.

12. SUBJID (b) (6)
67 y/o man with stage IV extranodal MZL who committed suicide during the pretreatment period. No autopsy was performed.

Reviewer's assessment: The clinical team agrees with the Applicant's assessment.

Serious Adverse Events

Data:

Table 3635: Applicant - Serious TEAEs by SOC and PT (≥ 2% of Subjects) - Liso-cel-treated Analysis Set

System Organ Class Preferred Term	3L+ R/R MZL (Cohort 4; N = 67); n (%)
Subjects With at Least One Serious TEAE	26 (38.8)
Immune System Disorders	14 (20.9)
CRS	13 (19.4)
Infusion Related Hypersensitivity Reaction	2 (3.0)
Nervous System Disorders	11 (16.4)
Aphasia	4 (6.0)
Tremor	3 (4.5)
Cognitive Disorder	2 (3.0)
Dizziness	2 (3.0)
Dysarthria	2 (3.0)
Dysgraphia	2 (3.0)
Transient Ischaemic Attack	2 (3.0)
Psychiatric Disorders	5 (7.5)
Confusional State	4 (6.0)
Blood and Lymphatic System Disorders	3 (4.5)
Neutropenia	2 (3.0)

Coded using MedDRA version 26.0. A subject was counted only once for multiple events within PT/SOC.
Source: ADSL, ADCORE, ADAE

The Applicant's Position:
In the 3L+ MZL Liso-cel-treated Analysis Set, 26 (38.8%) subjects experienced at least

one serious TEAE of any causality (Table 19). The most frequently reported serious TEAE was CRS (13 [19.4%] subjects). The occurrence of serious TEAEs is acceptable in this study population with R/R disease, and does not raise any concern for new safety signals.

The FDA's Assessment:

An SAE was defined as any adverse event (AE) occurring at any dose that:

- Results in death
- Is life threatening (i.e. in the opinion of the investigator, the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization of prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of the length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event (may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes).

Table 38 shows the serious adverse events observed in 3L+ MZL patients (n=67) with frequencies of >2% occurring within 90 days of treatment with liso-cel. These adverse reactions are reported based on FDA grouped terms (see Appendix XXX). Laboratory abnormalities such as neutropenia, lymphopenia, thrombocytopenia, and anemia are reported separately (under "Lab abnormalities" and are not included in this table). In the MZL cohort 4 of Study FOL-001, 39% of patients experienced a treatment emergent serious adverse event, most often due to cytokine release syndrome (19.4%), encephalopathy (10.45%), aphasia (7.46%), tremor (4.5%), sepsis (4.5%), and 3% each of dizziness, transient ischemic attack, and infusion related hypersensitivity. The FDA notes Grade ≥3 treatment emergent SAEs occurred in 14/67 or 21% of patients.

Both the original version of the protocol dated November 11, 2019 and the most recent version of the protocol dated October 11, 2024 require that the following conditions should be reported as SAEs regardless of relationship to study drug from the start of lymphodepleting chemotherapy through the end of the study:
- second primary malignancies
- new onset or exacerbation of a pre-existing neurologic disorder
- new onset of a rheumatologic or other autoimmune disorder
- new onset of a hematologic disorder
- rare and unexpected disorders with an unknown etiology (e.g. Guillain-Barre, Stevens-Johnson syndrome

The total number of patients who experienced a serious adverse event in the safety population on Study FOL-001 without regard to the treatment emergent window are captured in Table 39. Disorders belonging to the following systems are captured as an SAE:

- Neoplasms benign, malignant, and unspecified
- Nervous system disorders
- Psychiatric system disorders
- Immune system disorders
- Musculoskeletal and connective tissue disorders

Table 3637: FDA - FDA Summary of Treatment Emergent Serious Adverse Events in >2% of Patients

	N = 67 n (%)	**N=67 n (%)**
Serious Adverse Events	Any SAE n= 26 (39)	Grade 3-5 SAE n= 14 (21)
Immune system disorders CRS (by ASTCT)	13 (19.4)	2 (2.99)
Nervous system disorders Encephalopathy* Aphasia Tremor Delirium Dizziness Transient Ischemic Attack	7 (10.45) 5 (7.46) 3 (4.5) 2 (2.99) 2 (2.99) 2 (2.99)	- - - - - -
Infections and infestations Sepsis	3 (4.5)	2 (2.99)
General Infusion related hypersensitivity	2 (2.99)	-
Abbreviations: CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy ** Encephalopathy includes the preferred group terms confusional state, cognitive disorder, disturbance in attention, dysgraphia, brain fog, somnolence, memory impairment, dyscalculia, and amnesia Source: FDA Analysis		

Table 37 38: FDA - FDA Summary of Serious Adverse Events Regardless of Treatment Emergent Window in >2% of Patients

	N = 67 n (%)	**N=67 n (%)**
Serious Adverse Events	Any SAE n= 30 (45)	Grade 3-5 SAE n= 19 (28)
Immune system disorders CRS (by ASTCT)	13 (19.4)	2 (2.99)

Nervous system disorders		
Encephalopathy*	7 (10.45)	-
Aphasia	5 (7.46)	-
Tremor	3 (4.5)	-
Delirium	2 (2.99)	-
Dizziness	2 (2.99)	-
Transient Ischemic Attack	2 (2.99)	-
Infections and infestations		
Sepsis	3 (4.5)	2 (2.99)
COVID-19	4 (5.97)	4 (5.97)
Pneumonia	4 (5.97)	4 (5.97)
Febrile neutropenia	2 (2.99)	-
General		
Infusion related hypersensitivity	2 (2.99)	-
Fever	3 (4.48)	-
Neoplasms benign, malignant, and unspecified		
Nonmelanoma skin cancers	3 (4.48)	-
Acute myeloid leukemia	2 (2.99)	2 (2.99)
Squamous cell carcinoma	2 (2.99)	-

Abbreviations: CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy
* Neurotoxicity refers to the Applicant AE term "Neurotoxicity" defined as CAR-T-related Investigator-identified neurotoxicity events
** Encephalopathy includes the preferred group terms confusional state, cognitive disorder, disturbance in attention, dysgraphia, brain fog, somnolence, memory impairment, dyscalculia, and amnesia

Adverse Reactions

Data:

Table 3938: Applicant - Summary of Adverse Reactions Observed in ≥ 10% Subjects per Any Grade - 3L+ MZL Population in Study FOL-001

Adverse Reaction	**3L+ MZL (Cohort 4; N = 67); n (%)**		
System Organ Class **Preferred Term**	**Any Grade** **n (%)**	**Serious** **n (%)**	**Grade ≥ 3** **n (%)**
Immune system disorders			
Cytokine Release Syndrome	51 (76.1)	13 (19.4)	3 (4.5)
General disorders and administration site conditions			
Fatigue[a]	19 (28.4)	0	2 (3.0)
Edema[b]	12 (17.9)	1 (1.5)	2 (3.0)
Fever[c]	7 (10.4)	1 (1.5)	0
Nervous system disorder			
Headache	14 (20.9)	1 (1.5)	1 (1.5)
Encephalopathy[d]	13 (19.4)	6 (9.0)	1 (1.5)
Tremor	13 (19.4)	3 (4.5)	0
Dizziness[e]	11 (16.4)	2 (3.0)	0

Table 3938: Applicant - Summary of Adverse Reactions Observed in ≥ 10% Subjects per Any Grade - 3L+ MZL Population in Study FOL-001

Adverse Reaction	3L+ MZL (Cohort 4; N = 67); n (%)		
System Organ Class Preferred Term	Any Grade n (%)	Serious n (%)	Grade ≥ 3 n (%)
Aphasia[f]	7 (10.4)	5 (7.5)	0
Gastrointestinal disorders			
Diarrhea	19 (28.4)	1 (1.5)	1 (1.5)
Nausea	12 (17.9)	1 (1.5)	1 (1.5)
Abdominal Pain[g]	7 (10.4)	0	0
Metabolism and nutrition disorders			
Decreased appetite	7 (10.4)	1 (1.5)	2 (3.0)
Infections and infestations			
Infections - pathogen unspecified[h]	11 (16.4)	6 (9.0)	4 (6.0)
Psychiatric disorders			
Delirium[i]	7 (10.4)	2 (3.0)	2 (3.0)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[j]	15 (22.4)	0	0
Vascular disorders			
Hypotension	7 (10.4)	0	0
Renal and urinary disorders			
Renal failure[k]	7 (10.4)	1 (1.5)	1 (1.5)

[a] Fatigue includes Asthenia, Fatigue.
[b] Edema includes Ascites, Fluid retention, Hypervolemia, Edema peripheral, Peripheral swelling, Pleural effusion, Pulmonary edema.
[c] Fever includes Pyrexia.
[d] Encephalopathy includes Cognitive disorder, Confusional state, Disturbance in attention, Dyscalculia, Memory impairment, Somnolence.
[e] Dizziness includes Dizziness, Presyncope.
[f] Aphasia includes Aphasia, Dysarthria.
[g] Abdominal pain includes Abdominal distension, Abdominal pain, Abdominal pain upper.
[h] Grouped per high-level grouped term.
[i] Delirium includes Delirium, Disorientation, Hallucination, Irritability, Restlessness.
[j] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Flank pain, Neck pain, Non-cardiac chest pain, Pain in extremity.
[k] Renal failure includes Acute kidney injury, Blood creatinine increased.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with BREYANZI include the following:

- Blood and lymphatic system disorders: Febrile neutropenia (3.0%).
- Immune system disorders: Hemophagocytic lymphohistiocytosis (4.5%).
- General disorders and administration site conditions: Chills (7.5%).
- Nervous system disorders: Motor dysfunction[l] (4.5%), Ataxia[m] (3.0%), Neuropathy peripheral[n] (3.0%), Dysgeusia (1.5%).
- Gastrointestinal disorders: Vomiting (9.0%), Constipation (3.0%), Dyspepsia (3.0%).
- Metabolism and nutrition disorders: Tumor lysis syndrome (1.5%).
- Infections and infestations: Sepsis[o] (7.5%), Bacterial infectious disorders[p] (6.0%), Viral infectious disorders[p] (6.0%),
- Upper respiratory tract infection[q] (4.5%), Fungal infectious disorders[p] (3.0%), Urinary tract infection (3.0%), Pneumonia (1.5%).
- Psychiatric disorders: Insomnia (9.0%), Anxiety (4.5%).

- Vascular disorders: Hemorrhage[r] (9.0%), Hypertension (6.0%), Thrombosis[s] (3.0%).
- Respiratory, thoracic and mediastinal disorders: Dyspnea (6.0%), Cough (4.5%), Hypoxia (4.5%).
- Skin and subcutaneous tissue disorders: Rash[t] (4.5%).
- Cardiac disorders: Tachycardia[u] (7.5%).

[l] Motor dysfunction includes Fine motor skill dysfunction, Muscle spasms, Muscular weakness.
[m] Ataxia includes Coordination abnormal, Gait disturbance.
[n] Neuropathy peripheral includes Paresthesia, Peripheral sensory neuropathy.
[o] Sepsis includes Bacteremia, Neutropenic sepsis, Sepsis, Staphylococcal bacteremia, Staphylococcal sepsis.
[p] Grouped per high-level grouped term.
[q] Upper respiratory tract infection includes Nasopharyngitis, Sinusitis, Upper respiratory tract infection.
[r] Hemorrhage includes Contusion, Cystitis hemorrhagic, Epistaxis, Hematoma, Upper gastrointestinal hemorrhage.
[s] Thrombosis includes Deep vein thrombosis, Pulmonary embolism.
[t] Rash includes Rash maculo-papular, Rash pruritic, Urticaria.
[u] Tachycardia includes Sinus tachycardia, Tachycardia.

Source: ISS - ADSL, ISS - ADAE

The Applicant's Position

The most common nonlaboratory adverse reactions (≥ 20%) were CRS, fatigue, headache, diarrhea, and musculoskeletal pain (**Table 20).**

The FDA's Assessment:

During the safety review, adverse drug reactions (ADRs) are defined as any treatment emergent adverse event (TEAE) with onset or worsening after the start of lisocel infusion until day 90 regardless of perceived relationship and causality with lisocel. Ninety-one days after liso-cel infusion, only AEs related to any study procedure or liso-cel were collected.

The Applicant reported AEs by preferred terms, which may underestimate the incidence of some AEs. To minimize such underestimation of AE, FDA grouped preferred terms that represent the same disease process (see list of FDA group terms used for AE analysis below). 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.

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 will also have Grade 4 or 5 events.

The FDA agrees with the Applicant's summary of safety in MZL Cohort 4 of Study FOL-001 except as follows:

- IRR: SUBJID (b) (6) experienced a grade 1 infusion related hypersensitivity reaction on day 1 and SUBJID (b) (6) experienced a grade 2 infusion related hypersensitivity reaction on day 1.

- Autoimmune disorders: subject SUBJID (b) (6) developed a systemic granulomatous process involving the skin, eyes, joints, liver, and lungs that required immunosuppressives. Although the disorder was not formally diagnosed as an autoimmune disorder and the patient ultimately died of a Klebsiella pneumonia while on a JAK inhibitor, the clinical picture was concerning for underlying autoimmune disorder. See section 8.2.4 for additional details.

A separate FDA analysis of TEAE using FDA grouped preferred terms is displayed in Table 40 by system organ class and by decreasing order of incidence in Table 41. FDA recommends including these in section 6.1 of the USPI. How each grouped term was defined is outlined in Appendix XXX. The most common TEAEs (excluding laboratory abnormalities) (>20%) were cytokine release syndrome, fatigue, diarrhea, musculoskeletal pain, encephalopathy, headache, and tremor. The most common grade 3 or 4 adverse events (>3%) were cytokine release syndrome, hemophagocytic syndrome, and sepsis. For laboratory abnormalities, see the Laboratory Findings section.

Table 4039: FDA -FDA Summary of Treatment Emergent Adverse Events >5%

System Organ Class and Preferred Term	**Safety N=67 n (%)**	**Safety N=67 n (%)**
	All Grades	Grade 3-4
Immune system disorders		
CRS (ASTCT)	51 (76)	3 (4.5)
Hemophagocytic lymphohistiocytosis	3 (4.5)	3 (4.5)
Nervous system disorders		
Encephalopathy	14 (20.9)	1 (1.49)
Headache	14 (20.9)	1 (1.49)
Tremor	14 (20.9)	-
Dizziness	11 (16.4)	-
Aphasia	7 (10.45)	-
Delirium	7 (10.45)	2 (2.99)
Insomnia	6 (9)	-
Fall	5 (7.5)	-
General disorders and administration site conditions		
Fatigue	19 (28.4)	2 (2.99)
Pyrexia	7 (10.45)	-
Edema	12 (17.9)	2 (2.99)
		-

Chills	5 (7.5)	
Gastrointestinal disorders Diarrhea Nausea Abdominal pain Vomiting	 19 (28.4) 12 (17.9) 6 (8.96) 6 (8.96)	 1 (1.49) 1 (1.49) - -
Musculoskeletal and connective tissue disorders Musculoskeletal pain	 15 (22.4)	 -
Renal and Urinary disorders Renal insufficiency	 7 (10.45)	 1 (1.49)
Metabolism and nutrition disorders Decreased appetite Dehydration	 7 (10.45) 4 (6)	 2 (2.99) -
Vascular disorders Hypotension Hypertension Thrombosis	 7 (10.45) 4 (6) 4 (6)	 - 2 (2.99)1 (1.49)
Respiratory, thoracic, and mediastinal disorders Dyspnea	 4 (6)	 -
Infections and Infestations Sepsis	 5 (7.5)	 3 (4.48)
Skin and subcutaneous tissue disorders Xerosis	 4 (6)	 -
Abbreviations: CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy; Source: FDA analysis		

Table 4041: FDA - Summary of Treatment Emergent Adverse Events -FOL-001 MZL Cohort

FDAGT*	All grade, N	All grade, %	Grade 3 or higher, N	Grade 3 or higher, %
Cytokine release syndrome	51	76.12%	3	4.48%
Diarrhoea	19	28.36%	1	1.49%
Fatigue	18	26.87%	2	2.99%
Leukopenia	15	22.39%	13	19.40%
Musculoskeletal pain	15	22.39%	0	0.00%

Headache	14	20.90%	1	1.49%
Tremor	14	20.90%	0	0.00%
Encephalopathy	13	19.40%	1	1.49%
Edema	12	17.91%	2	2.99%
Nausea	12	17.91%	1	1.49%
Dizziness	11	16.42%	0	0.00%
Infection- Pathogen unspecified	9	13.43%	4	5.97%
Abdominal pain	7	10.45%	0	0.00%
Aphasia	7	10.45%	0	0.00%
Decreased appetite	7	10.45%	2	2.99%
Delirium	7	10.45%	2	2.99%
Fever	7	10.45%	0	0.00%
Hypotension	7	10.45%	0	0.00%
Renal failure	7	10.45%	1	1.49%
Hemorrhage	6	8.96%	1	1.49%
Insomnia	6	8.96%	0	0.00%
Vomiting	6	8.96%	0	0.00%
Affective disorder	5	7.46%	0	0.00%
Bacterial infection	5	7.46%	1	1.49%
Chills	5	7.46%	0	0.00%
Fall	5	7.46%	0	0.00%
Tachycardia	5	7.46%	0	0.00%
Chest pain	4	5.97%	0	0.00%
Dehydration	4	5.97%	0	0.00%
Dyspnoea	4	5.97%	0	0.00%
Hypertension	4	5.97%	2	2.99%
Thrombosis	4	5.97%	1	1.49%
Viral infection	4	5.97%	1	1.49%
Xerosis	4	5.97%	0	0.00%
Cough	3	4.48%	0	0.00%
Haemophagocytic lymphohistiocytosis	3	4.48%	3	4.48%
Hypoxia	3	4.48%	0	0.00%
Motor dysfunction	3	4.48%	0	0.00%
Oral pain	3	4.48%	0	0.00%
Rash	3	4.48%	1	1.49%
Weight decreased	3	4.48%	0	0.00%
Alopecia	2	2.99%	0	0.00%
Ataxia	2	2.99%	0	0.00%
Constipation	2	2.99%	0	0.00%
Disseminated intravascular coagulation	2	2.99%	0	0.00%
Dyspepsia	2	2.99%	0	0.00%
Ear pain	2	2.99%	0	0.00%
Febrile neutropenia	2	2.99%	2	2.99%
Fungal infection	2	2.99%	0	0.00%
Inflammation	2	2.99%	0	0.00%
Infusion related hypersensitivity reaction	2	2.99%	0	0.00%

Neuropathy peripheral	2	2.99%	1	1.49%
Sinus bradycardia	2	2.99%	0	0.00%
Transient ischaemic attack	2	2.99%	0	0.00%
Atelectasis	1	1.49%	0	0.00%
Axillary pain	1	1.49%	0	0.00%
Breath sounds abnormal	1	1.49%	0	0.00%
Catheter site pain	1	1.49%	0	0.00%
Cerumen impaction	1	1.49%	0	0.00%
Decubitus ulcer	1	1.49%	0	0.00%
Dysphagia	1	1.49%	0	0.00%
Excessive cerumen production	1	1.49%	0	0.00%
Facet joint syndrome	1	1.49%	1	1.49%
Failure to thrive	1	1.49%	1	1.49%
Gastritis	1	1.49%	0	0.00%
Gastrooesophageal reflux disease	1	1.49%	0	0.00%
Haemorrhoids	1	1.49%	0	0.00%
Hiccups	1	1.49%	0	0.00%
Lung infiltration	1	1.49%	1	1.49%
Lymphadenopathy	1	1.49%	0	0.00%
Meningioma	1	1.49%	0	0.00%
Nasal discomfort	1	1.49%	0	0.00%
Ocular discomfort	1	1.49%	0	0.00%
Pain	1	1.49%	0	0.00%
Polyuria	1	1.49%	0	0.00%
Proctalgia	1	1.49%	0	0.00%
Pruritus	1	1.49%	0	0.00%
Scrotal injury	1	1.49%	0	0.00%
Seborrhoeic keratosis	1	1.49%	0	0.00%
Skin lesion	1	1.49%	0	0.00%
Subdural hygroma	1	1.49%	0	0.00%
T-cell lymphoma	1	1.49%	1	1.49%
Tinnitus	1	1.49%	0	0.00%
Tumour lysis syndrome	1	1.49%	0	0.00%
Urinary incontinence	1	1.49%	0	0.00%
Urinary retention	1	1.49%	0	0.00%
Vitamin D deficiency	1	1.49%	0	0.00%
Source: FDA analysis of ADAE data-Study FOL-001 MZL Cohort *FDAGT represents grouped PTs (see Appendix)				

Adverse Events of Special Interest (AESI)

Data:
AESI frequencies are summarized in Table 17.

CRS

The Applicant's Position:
In the Liso-cel-treated Analysis Set, CRS occurred in 76.1% subjects, including Grade 3

CRS in 4.5% of subjects. There were no subjects with Grade 4 or Grade 5 CRS events (Table 17). The most common any grade treatment-emergent CRS symptoms (≥ 10% subjects) included pyrexia (76.1%), hypotension (25.4%), and chills (19.4%) (ADSL, ADCORE, ADAE, ADCRSNT). The median time to CRS onset from the time of liso-cel infusion was 4 days (range: 1 to 29 days). The upper bound of the range of time to CRS onset was due to one subject with a Grade 1 CRS event. CRS resolved in all subjects; the median time to resolution was 4 days (range: 1 to 13 days) (Table 17) (ADSL, ADCORE, ADAE, ADCRSNT).

The FDA's Assessment:
The FDA verified that 51/67 (76%) 3L+ MZL patients who receiving conforming product experienced any grade CRS with 43/67 (64%) experiencing grade 1 CRS, 18/67 (26.9%) experiencing grade 2 CRS, and 3/67 (4.48%) experienced grade 3 CRS(4.48%). Fifty-one out of 67 patients (76%) experienced pyrexia, 17/67 patients experienced hypotension (25.4%), and 13/67 patients experienced chills (19.4%). The median time to CRS onset was 4 days (range: 1 to 29 days) and the median duration of CRS was 4 days (1, 13) as noted by the Applicant.

The FDA also searched ADAE data to identify any subjects with CRS symptoms of fever, hypotension, and/or hypoxia between day 0 and 30 who were not flagged as having CRS. The FDA confirmed that all patients presenting with an AE of fever (n=7), hypotension (n=7), hypoxia (n=2), and hypoxemia (n=1) in the ADAE dataset between days 0 and 30 were also captured as having CRS. Of note, there were a total of 37/51 (73%) patients who received tocilizumab to treat their CRS. The only patient who received tocilizumab but was not captured as having an AE of CRS was patient USUBJID (b) (6) who received nonconforming product. Subject (b) (6) was a 77-year-old woman with stage 4 splenic marginal zone lymphoma who received nonconforming product on day 1. The patient presented with grade 1 pyrexia on day -5 in the setting of patchy lung opacities bilaterally on imaging and moderate to large malignant pleural effusions. The pyrexia resolved on day -3. The patient subsequently experienced grade 3 CRS and grade 1 investigator-identified neurologic toxicity on day 4 requiring tocilizumab and decadron between days 4 and day 9. Other non-laboratory AEs included grade 2 insomnia on day 1 and grade 3 hypoxia on day 2 in the setting of the pleural effusions that required lasix, bilateral thoracentesis (day 3 on left and day 4 on right), and bilateral pleurodesis (day 6 on left and day 45 on right).

Neurologic Toxicity (specific to the product class)
The Applicant's Position:
In the Liso-cel-treated Analysis Set, iiNT occurred in 32.8% of subjects, including Grade 3 iiNT in 4.5% of subjects. There were no subjects with Grade 4 or Grade 5 iiNT events (Table 17). The most common any grade iiNTs by PT (≥ 10% subjects) was tremor (14.9%) (ADSL, ADCORE, ADAE, ADCRSNT). The median time to iiNT onset from the time of liso-cel infusion was 8.5 days (range: 2 to 36 days). The upper bound of the range of time to onset was due to one subject having Grade 1-2 iiNT symptoms (tremor) (ADSL,

ADCORE, ADAE, ADCRSNT). iiNT resolved in all subjects; the median time to resolution was 8.0 days (range: 1 to 90 days).[30] The upper bound of the range of time to resolution was due to one subject having a Grade 1 iiNT symptom (tremor), which lasted 90 days (Table 17) (ADSL, ADCORE, ADAE, ADCRSNT).

The FDA's Assessment:

The Applicant used the AE term "Neurotoxicity" to capture CAR-T-related Investigator-identified neurotoxicity events (ii-NT). Any iiNT events occurring within 7 days were considered in a single episode. The time to resolution for investigator-identified events was defined when the last investigator-identified event of the 1st episode ended. Importantly, subjects with an unresolved event in the episode were excluded from the calculation of time to resolution. Symptoms of neurotoxicity were graded using NCI CTCAE v.5.

The review team defined adverse drug reactions as any treatment emergent adverse event (TEAE) occurring after the start of liso-cel infusion regardless of the perceived relationship and causality with liso-cel. In the Applicant's response to an FDA Information Request dated December 2, 2025, the Sponsor clarified the inclusion of a separate category of Neurological Toxicity in the ADAE dataset defined as adverse events belonging to the Nervous System Disorders or Psychiatric System Disorders SOC, regardless of investigator assessment of relatedness.

Out of 67 3L+ MZL subjects, 22 subjects (32.8%) experienced the Applicant's prespecified definition of "Investigator-identified neurotoxicity". The nature of the neurologic toxicity captured by "Investigator-identified neurotoxicity" was described in the ADCRSNT dataset and is shown below in Table 42. Among 22 subjects with prespecified "investigator-identified neurotoxicity", tremor was the most frequent investigator-identified neurotoxicity, occurring at an incidence of 14.9%. Using FDA preferred group terms which group brain fog, cognitive disorder, confusional state, disturbance in attention, dysgraphia, dyscalculia, somnolence, and memory impairment under encephalopathy, the incidence of encephalopathy is, in fact, the most frequent symptom of investigator-identified neurotoxicity at 17/67 or 25%.

Table 4142: FDA -FDA Summary of Clinical Symptoms Associated with Investigator Identified Neurotoxicity

TEAE	**Lisocabtagene maraleucel N=67 n (%)**	
	Grade 1-5 n (%)	Grade 3-5 n (%)
Tremor	10 (14.9)	0

Confusional state	6 (9)	1 (1.5)
Disorientation	4 (6)	1 (1.5)
Aphasia	6 (9)	0
Headache	3 (4.5)	1 (1.5)
Cognitive disorder	3 (4.5)	0
Delirium	2 (3)	0
Dizzyness	2 (3)	0
Dysarthria	2 (3)	0
Dysgraphia	2 (3)	0
Brain fog	1 (1.5)	0
Chills	1 (1.5)	0
Coordination abnormality	1 (1.5)	0
Disturbance in attention	1 (1.5)	0
Dyscalculia	1 (1.5)	0
Dysdiadochokinesis	1 (1.5)	0
Fine motor skill dysfunction	1 (1.5)	0
Gait disturbance	1 (1.5)	0
Hallucination	1 (1.5)	0
Intention tremor	1 (1.5)	0
Peripheral sensory neuropathy	1 (1.5)	1 (1.5)
Somnolence	1 (1.5)	0
Urinary incontinence	1 (1.5)	0

There were an additional 41 patients (61%) with treatment emergent nervous system and psychiatric system disorders (i.e. neurological toxicity) in the ADAE dataset (as shown in Table 43) and 47 patients (70%) with nervous system and psychiatric system disorders captured both within and outside the treatment emergent window (as shown in

Table 42). The review team acknowledges that neurological toxicity referring to adverse events of headache, dizziness, insomnia, anxiety, depression, peripheral neuropathy, and TIA may be attributable to etiologies other than liso-cel. However, the clinical review team attributes subjects with the following adverse events termed neurological toxicity as potentially attributable to liso-cel:

1. Tremor
   a. Treatment emergent SUBJID (b) (6) ; grade 1; 2 days (day 10-11)
   b. Treatment emergent SUBJID (b) (6) ; grade 1; 165 days (day 26-190)
   c. Treatment emergent SUBJID (b) (6) ; grade 2; 57 days (day 11- 67)
   d. Treatment emergent SUBJID (b) (6) ; grade 1; 4 days (day 5-8) and 49 days (day 11-67)
   e. Not treatment emergent SUBJID (b) (6) ; grade 1; 62 days (day -4 to day 58)
   f. Treatment emergent SUBJID (b) (6); grade 1; unresolved (day 20- 630; then day 630 to unresolved)
2. Encephalopathy:
   a. Treatment emergent SUBJID (b) (6) - grade 1; unresolved (unresolved from day 31)
   b. Treatment emergent SUBJID (b) (6) - grade 1; 28 days (day 12-39)
   c. Treatment emergent SUBJID (b) (6) - grade 1; unresolved (no start or end date)
   d. Treatment emergent SUBJID (b) (6) - grade 1; 140 days (day 30-169)
   e. Not treatment emergent SUBJID (b) (6) - grade 1; 133 days (day 164-296)
3. Delirium
   a. Treatment emergent SUBJID (b) (6) - grade 1; 23 days (day 9-31)
   b. Treatment emergent SUBJID (b) (6) - grade 3; unresolved
   b. Treatment emergent SUBJID (b) (6) - grade 1; 10 days (day 2-11)
4. Extensor Plantar Response
   a. Not treatment emergent SUBJID (b) (6) ; grade 1 unresolved
5. Subdural hygroma
   a. Treatment emergent SUBJID (b) (6) ; grade 1; unresolved
6. Taste disorder
   a. Treatment emergent SUBJID (b) (6) ; grade 1 (day 1-10)

Table 42. FDA Summary of All Nervous System and Psychiatric System Disorders Beyond 90 days from Liso-cel treatment among 67 Subjects in the MZL Cohort of Study FOL-001

Preferred Term	Safety N=67 n (%)	Safety N=67 n (%)
	All grades	Grades 3-4
Neurotoxicity	22 (32.8)	3 (4.48)
Headache	17 (25.4)	1 (1.49)
Tremor	15 (22.4)	0

Encephalopathy	**14 (20.9)**	**1 (1.49)**
Dizziness	**11 (16.4)**	**0**
Insomnia	**11 (16.4)**	**0**
Aphasia	**7 (10.5)**	**0**
Delirium	**7 (10.5)**	**2 (2.99)**
Anxiety	**4 (5.97)**	**0**
Peripheral neuropathy	**3 (4.48)**	**1 (1.49)**
Depression	**2 (2.99)**	**0**
TIA	**2 (2.99)**	**0**
Ataxia	**1 (1.49)**	**0**
Extensor Plantar	**1 (1.49)**	**0**
Motor dysfunction	**1 (1.49)**	**0**
Subdural hygroma	**1 (1.49)**	**0**
Taste disorder	**1 (1.49)**	**0**

The median duration of investigator-identified neurotoxicity was 3 days (range: 1, 90). The median duration of neurological toxicity (i.e. nervous system and psychiatric system disorder adverse events not captured as investigator-identified neurotoxicity was 11 days (range: 1, 611 days). The median time to resolution of investigator-identified neurotoxicity in the MZL cohort on Study FOL-001 was 9 days (range 1, 90), not 8 days as indicated by the Applicant. The Applicant maintains that investigator-identified neurotoxicity resolved in all subjects. In fact, grade 2 delirium, grade 3 encephalopathy, and grade 3 polyneuropathy were unresolved investigator-identified neurotoxicity in USUBJID (b) (6) . Brief narratives for subject (b) (6) with unresolved investigator-identified neurotoxicity and for 8 additional subjects with neurological toxicity which did not resolve are provided below.

1. SUBJID (b) (6) encephalopathy (disturbance in attention)
46 y/o woman with stage IV extranodal MALT lymphoma diagnosed in 2017 with day 9, grade 2 CRS (treated with tocilizumab), day 24 grade 1 dizziness (resolved day 66), day 31 prolonged grade 3 decreased ANC, and day 31 grade 1 disturbance in attention, developed progressive disease on day 164 followed by administration of NALT, with ongoing disturbance of attention at time of writing of the report.

2. SUBJID (b) (6) : encephalopathy (memory impairment)
67 y/o male with stage IV nodal MZL with day 1, grade 1 insomnia (resolved day 31), grade 1 memory impairment on unknown day in April 2023, day 7 grade 3 CRS (received tocilizumab; resolved day 9), day 7 investigator-identified neurotoxicity (grade 2 aphasia and grade 1 gait disturbance; treated with decadron on day 7-8; gait disturbance resolved on day 8); day 9 grade 1 insomnia and irritability (resolved day 31); day 14 grade 1 headache (resolved day 15). The subject received decadron between day 10 and day 31. Aphasia resolved on day 31. Memory impairment was

ongoing at time of writing of report and does not have an AE end date in the ADAE dataset.

3. SUBJID (b) (6) : anxiety
62 y/o man with stage IV nodal MZL with day 1, grade 1 infusion hypersensitivity reaction (resolved day 3) and pyrexia (resolved day 1), day 7 grade 1 headache which worsened to grade 2 on day 13 (resolved on day 29), day 8 grade 1 CRS (resolved day 10), day 16 grade 3 pleural effusion requiring day 17 right sided thoracentesis (resolved day 25), day 19 grade 2 presyncope (resolved day 19), and day 29 grade 1 anxiety which did not resolve at time of writing of report. ADAE dataset has no end date for anxiety.

4. SUBJID (b) (6) : insomnia
76 y/o with stage IV splenic zone MZL, with day 1 grade 2 infusion related hypersensitivity reaction (treated with tocilizumab and decadron and resolved on day 2), day 7 grade 1 CRS that worsened to grade 2 on day 8 (treated with tocilizumab and decadron, resolved on day 8, received anakinra prophylactically on day 9), day 9 investigator-identified neurologic toxicity (grade 1 tremor treated with decadron through day 10, anakinra prophylactically from day 9 through day 12, levetiracetam prophylactically from day 9 to day 16, resolved on day 11), grade 3 decreased platelet count on day 29 (resolved to grade 1 on day 92). Grade 1 insomnia occurred on day -2 in ADAE dataset and had no end date. Insomnia was not described in patient narrative.

5. SUBJID (b) (6) : insomnia with no end date due to patient death
50 y/o woman with stage IV nodal MZL with grade 1 CRS that worsened to grade 2 on day 8 (treated with tocilizumab and resolved on day 9), with grade 2 abdominal pain on day 20, grade 4 T cell lymphoma diagnosed retrospectively on day 22, grade 1 insomnia on day 23, followed by the patient's death on day 32 due to T cell lymphoma.

6. SUBJID (b) (6) : tremor
57 y/o with stage 2 extranodal MALT MZL with day 4 grade 1 CRS (resolved day 13), day 11 investigator-identified neurological toxicity (grade 1 headache and grade 1 tremor). Patient had a resting and intentional tremor in the arms. Investigator-identified neurotoxicity (tremor and headache) resolved day 19. Day 20 grade 1 tremor persisted and worsened to grade 2 on day 631 (as described in the narrative). There was no AE end date for the grade 2 tremor in the ADAE dataset.

7. SUBJID (b) (6) : neurotoxicity, peripheral neuropathy, subdural hygroma
71 y/o man with stage 4 splenic MZL who died on day 47 due to neutropenic sepsis with ongoing events of delirium, confusion, restlessness, and subdural hygroma. The patient developed grade 3 peripheral neuropathy complicated by a fall on day 16, grade 3 confusional state on day 17, and grade 1 aphasia on day 18. MRI brain showed a 1.5 cm left frontal meningioma. Patient received intravenous decadron (in addition to risperidone and quetiapine) for neurotoxicity which waxed and waned between a grade

2 confusional state and grade 3 confusional state before resolving on day 36, the day of hospital discharge. The patient was readmitted on day 42 with grade 3 neutropenic sepsis and grade 3 confusional state. "The subject did not respond to communication but was awake, further described as grade 4 ICANS considered by the investigator to be due to neutropenic sepsis". The patient developed grade 3 restlessness on day 43 which is the same day blood cultures became positive for Klebsiella pneumoniae and E.coli for which he received broad spectrum antibiotics. The patient was subsequently diagnosed with a grade 1 subdural hygroma on day 46 in addition to receiving a diagnosis of diabetes insipidus before his death on day 47 with ongoing events of delirium, confusion, restlessness, and subdural hygroma as previously described. There was no AE end date for the following investigator-identified neurotoxicities: grade 3 peripheral neuropathy, grade 3 confusion, and grade 2 delirium.

8. SUBJID (b) (6) : extensor plantar response; not treatment emergent
55 y/o man with stage 3 extranodal MALT MZL with day 1 grade 1 anxiety treated with a benzodiazepine (resolved day 17), day 5 grade 2 CRS (treated with tocilizumab on day 6 after which CRS resolved), day 5 grade 3 Staphylococcal sepsis (resolved day 13), day 14 investigator-identified neurologic toxicity (grade 1 disorientation and headache; resolved on day 15), day 29 prolonged cytopenia with grade 3 decreased platelets (improved to grade 1 on day 58). Extensor plantar response is not described in narrative. AE end date is not documented in ADAE dataset.

Analysis of neurologic toxicity using FDA Grouped Terms

A total of 41/67 (61%) subjects developed symptoms involving nervous or psychiatric system. A total of 22/67 (33%) subjects were flagged as having neurotoxicity including grade 3 NT in 3/67 (4%). No grade 4 or 5 NT symptoms occurred.

In order to characterize the neurologic toxicity which occurred following treatment with liso-cel, MedDRA PTs for AEs involving Nervous system and psychiatric system (AEBODYSYS) were grouped. The frequency of these neurologic AEs are summarized in Table below:

Table 4343 : FDA - Analysis of neurologic toxicity using FDA Grouped Terms

FDAGT	All grade, N	All grade, %	Grade 3 or higher, N	Grade or higher, %
Neurotoxicity	22	32.84%	3	4.48%
Neurotoxicity symptoms				
Headache	14	20.90%	1	1.49%
Tremor	14	20.90%	0	0.00%

Encephalopathy	13	19.40%	1	1.49%
Dizziness	11	16.42%	0	0.00%
Aphasia	7	10.45%	0	0.00%
Delirium	7	10.45%	2	2.99%
Insomnia	6	8.96%	0	0.00%
Affective disorder	5	7.46%	0	0.00%
Ataxia	2	2.99%	0	0.00%
Neuropathy peripheral	2	2.99%	1	1.49%
Transient ischaemic attack	2	2.99%	0	0.00%
Motor dysfunction	3	4.48%	0	0.00%
Subdural hygroma	1	1.49%	0	0.00%

Source: FDA analysis of ADAE data-Study FOL-001 MZL Cohort
FDAGT grouped preferred terms as below:
Affective disorder: Anxiety, depression, depressed mood
Aphasia: Aphasia, dysarthria
Ataxia: impaired coordination, gait disturbance
Delirium: delirium, disorientation, irritability, hallucination
Dizziness: Dizziness, presyncope
Encephalopathy: amnesia, coordination abnormal, confusional state, dyscalculia, dysgeusia, dysgraphia, cognitive disorder, Disturbance in attention, brain fog, somnolence
Motor dysfunction: dysdiadochokinesis, Fine motor skill dysfunction, muscle spasms, muscle weakness
Neuropathy peripheral: Peripheral sensory neuropathy, paresthesia
Tremor: tremor, intention tremor

Prolonged Cytopenia

The Applicant's Position:
Prolonged cytopenia, defined as ≥ Grade 3 cytopenia at the Day 29 (+/- 2 days) visit based on laboratory assessments of neutropenia, thrombocytopenia, or anemia, occurred in 28 (41.8%) of 3L+ MZL subjects in the Liso-cel-treated Analysis Set (Table 17). The majority of subjects recovered from prolonged cytopenia by Day 90 (ADSL, ADCORE, ADCPT).

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). Out of 67 treated MZL patients, 65 (97%) patients had any grade decreased hemoglobin, platelet or neutrophil count at day 29

day visit (+/-2 window). Grade 3 or higher prolonged cytopenias persisted in 40% (27/67) patients, including thrombocytopenia in 21%, neutropenia in 27% and anemia in 9% of patients.

Table 4444: FDA - Summary of Persistent Cytopenia in MZL patients in Study FOL-001 (N=67)

PARAM_FDA	All grade, N	All grade, %	Grade 3 or higher, N	Grade 3 or higher, %
Hemoglobin decreased at day 29 (+-2 days)	65	97%	6	9%
Neutrophil decreased at day 29 (+-2 days)	65	97%	18	27%
Platelet decreased at day 29 (+-2 days)	65	97%	14	21%
Source: FDA Analysis of ADLB data from FOL-001 Study.				

Infections

The Applicant's Position:

In the 3L+ MZL Liso-cel-treated Analysis Set, Grade ≥ 3 infections were reported in 6 (9.0%) subjects. The most common Grade 3-4 infection and infestation by PT was infections - pathogen unspecified (ADSL, ADCORE, ADAE). There was 1 (1.5%) Grade 5 infection and infestation TEAE (neutropenic sepsis) in the 3L+ MZL Liso-cel-treated Analysis Set (ADSL, ADCORE, ADAE).

The FDA's Assessment:

When analyzing the ADAE dataset by Organ Class there were a total of 18 out of 67 subjects who experienced an infection or infestation, i.e. 27%, and 6 out of 67 (9%) subjects who experienced a grade 3 or greater infection. Table 45 describes all infections and infestations that occurred within the treatment emergent window for the MZL cohort in Study FOL-001.

Table 4545: FDA Summary of Treatment Emergent Infections and Infestations in MZL Cohort in Study FOL-001

Infection and infestation	All grade	Grade 3
Total	18 (27)	6 (9)

Sepsis	5 (7.5)	3 (4.5)
COVID-19	3 (4.48)	1 (1.49)
Respiratory tract infection	2 (2.99)	0
Upper respiratory tract infection	2 (2.99)	1 (1.49)
Urinary tract infection	2 (2.99)	0
Balanitis candida	1 (1.49)	0
Device related infection	1 (1.49)	0
Enterocolitis bacterial	1 (1.49)	0
Folliculitis	1 (1.49)	0
Infection	1 (1.49)	0
Nasopharyngitis	1 (1.49)	0
Oral candidiasis	1 (1.49)	0
Pneumonia	1 (1.49)	1 (1.49)

Table 4646: FDA - summary of FDA analysis of infections that occurred following treatment with liso-cel

FDAGT	All grade, N	All grade, %	Grade 3 or higher, N	Grade 3 or higher, %
Infections - pathogen unspecified	11	16%	5	7%
Viral infection	9	13%	5	7%
Bacterial infection	7	10%	2	3%
Fungal infection	3	4%	1	1%

Infections – pathogen unspecified: per AEHLGT
Bacterial infection: Folliculitis, enterocolitis bacterial, bacteremia, superinfection bacterial, staphylococcal bacteremia, pneumonia streptococcal, staphylococcal sepsis
Fungal infection: Pneumocystis jirovecii pneumonia, oral candidiasis, balanitis candida
Viral infection: COVID-19, COVID-19 pneumonia, influenza, pneumonia cytomegaloviral, viral sinusitis

Hypogammaglobulinemia

The Applicant's Position:

Overall, incidences of hypogammaglobulinemia AESIs were low (Table 17) and the majority were mild to moderate in severity (Grade 1-2).

The FDA's Assessment:

The FDA notes three events of hypogammaglobulinemia in the ADAE dataset, one that was treatment-emergent, for a total rate of 4.5%.

MAS

The Applicant's Position:

In the 3L+ MZL Liso-cel-treated Analysis Set, there were 3 subjects who reported an event of MAS, all were Grade 3 (Table 17).

The FDA's Assessment:

The FDA reviewed the 3 events of hemophagocytic lymphohistiocytosis as described by the Applicant. Secondary HLH in patients with underlying lymphoma typically manifests as a critical illness with sepsislike manifestations. The short course of symptoms in subject (b) (6) and subject (b) (6) and the clinical criteria used to diagnose subject (b) (6) are not typical for how a diagnosis of HLH is made. The clinical team, however, defers to the investigator's evaluation.

- Subject (b) (6) was a 71 year old male with stage IV splenic MZL. The subject experienced day 1 grade 1 CRS treated with tocilizumab on day 2 and day 6, decadron from day 2 through day 10, and anakinra from day 6 to day 17. The subject was diagnosed with grade 3 HLH based on an elevated LDH, triglycerides, and ferritin on day 7 for which he received phytomenadione. Day 8, he experienced grade 1 tremor and urinary incontinence and grade 3 disorientation which resolved by day 10. CRS resolved on day 10, and HLH resolved on day 12. However, grade 1 aphasia occurred on day 14 but resolved by day 18. The subject was diagnosed with a grade 2 TIA on day 19 though it is unclear why his dysarthria, aphasia, and abnormal sensations in his right hand weren't considered part of the neurotoxicity he'd already experienced. Grade 1 aphasia and grade 1 cognitive disorder recurred on day 25.
- Subject (b) (6) was a 57 y/o female with stage IV splenic MZL who developed grade 2 hypotension on day 1, grade 2 hypoxia on day 3, grade 1 CRS on day 3 which increased to grade 2 by day 5 (treated with paracetamol, tocilizumab, and decadron and resolved by day 7), self-limited hypoxia on day 8, grade 2 presyncope on day 21, prolonged cytopenia with grade 3 decreased hemoglobin on day 29, with day 32 grade 3 HLH treated with anakinra, with resolution of HLH

by day 42. Clinical decisionmaking around diagnosis of HLH on day 32 was not provided.

- Subject (b) (6) is a 72 y/o male with stage 4 nodal MZL with CRS that ranged from grade 1 on day 1 (treated with paracetamol and resolved day 4) to grade 2 on day 6 (treated with paracetamol, tocilizumab, and oxygen and resolved day 9). The subject also experienced grade 2 hypotension on day 1 treated with fluids (resolved day 4). Grade 3 acute kidney injury occurred on day 8 with worsening hypotension in the setting of presumed CRS requiring an additional dose of tocilizumab. The patient was transferred to the ICU for dialysis on day 10 for grade 1 tumor lysis syndrome though lab criteria were not provided. CRS subsequently resolved, but day 10, the subject received a diagnosis of grade 3 HLH based on an IL2 receptor of 96.3, an elevated AST, and ferritin. The patient received treatment for both CRS and HLH with cryoprecipitate on day 10, factor 1/8/13/vWF on day 10 and 14, and decadron from day 8 to day 11. On day 16, the subject's IL2 receptor was 8130. Since tumor lysis syndrome resolved on day 18, dialysis ceased on day 21. The patient remained on steroids through day 38 for HLH. On day 33, the subject experienced a grade 1 confusional state (resolved day 38) and dysarthria (resolved day 46) and was hospitalized day 37 with memory loss. The subject resumed steroids on day 38 and continued on them through day 80 when HLH was felt to have resolved. Clinical criteria used to diagnose HLH are unclear as is the rationale for the approach to treatment of HLH which was inconsistent with the standard of care (i.e. use of factor replacement).

IRR

The Applicant's Position:
There were no incidences of IRR (Table 17).

The FDA's Assessment:
The FDA disagrees with the Applicant. There were two patients with an infusion-related hypersensitivity reaction, i.e. SUBJID (b) (6) (grade 1 infusion related hypersensitivity reaction) and SUBJID (b) (6) (grade 2 infusion related hypersensitivity reaction).

TLS

The Applicant's Position:
There was 1 incidence of Grade 1 TLS (Table 17).

The FDA's Assessment:
The FDA notes this event of grade 1 tumor lysis syndrome occurred on day 9 in a patient with stage 4 nodal MZL (subject (b) (6)). The subject, in fact, experienced 2 episodes of CRS: one grade 1 episode one day 1 that required fluids for grade 2 hypotension and paracetamol for fevers and chills and resolved by day 4 and one grade 1 episode on day 5 that worsened to grade 2 and required paracetamol, tocilizumab, and oxygen. The subject developed grade 3 acute kidney injury on day 8 and received

a second dose of tocilizumab as well as dexamethasone. The CRS resolved by day 9, the same day that grade 1 tumor lysis was diagnosed. The subject received rasburicase, allopurinol, and acetylcysteine; calcium chloride, potassium chloride, and sodium lactate; and dialysis on day 11, day 12, and day 18 for the tumor lysis. Also on day 10, grade 3 hemophagocytic lymphohistiocytosis (HLH) was diagnosed for which the subject received decadron from day 8 to day 21 and factor replacements (factor 1, factor 8, factor 13, von Willebrand factor) which are an unusual treatment for HLH. IL2 receptor measured 8130 on day 16. The subject continued to receive decadron through day 80 for HLH at which time HLH was considered resolved. The subject's course was otherwise notable for day 38 neurotoxicity treated with decadron (fatigue, slurred speech, confusion, and memory loss) though day 37 head CT showed a right frontal 3 mm subdural hematoma subsequently managed conservatively.

Reviewer assessment: The cause of the renal failure appears multifactorial and tumor lysis cannot be ruled out. However, tumor lysis syndrome is a highly unusual complication of MZL, particularly on day 9 of treatment when it began on the same day that an episode of grade 2 CRS resolved.

SPM

The Applicant's Position:

SPM were reported in 8 (11.9%) 3L+ MZL subjects in the Liso-cel-treated Analysis Set (Table 17). Reported SPMs were MDS (1 subject), TCL (1 subject), AML (2 subjects), and skin cancers (squamous cell carcinoma, basal cell carcinoma or sebaceous carcinoma, 4 subjects).[30]

The frequency of all-grade SPMs during the post-treatment emergent period in the 3L+ MZL Treated Set was consistent with the published background incidence in this MZL population.[31] SEER data showed a cumulative incidence proportion of 12% for SPMs, not including NMSC.[32,33] One study placed the incidence at 16% including NMSC.[34]

Tumor samples from 4 of the 8 SPM subjects were tested; 2 were negative for transgene and 1 was unevaluable due to sample quality. In the remaining case (TCL), a low level of transgene was detected in the tumor, and insertion site analysis suggested that TCL was not associated with insertional mutagenesis.

The FDA's Assessment:

There was no evidence of insertional mutagenesis reported in the sBLA. Table 47 provides a summary of secondary malignancies followed by brief narrative descriptions.

Table 4747: FDA - Summary of Secondary Malignancies

USUBJID	Age/Sex	MZL Subtype	Cancer Type	Start Day After Liso-cel
(b) (6)	50 y/o woman	Nodal	T cell lymphoma	Day 22

(b) (6)				
	57 y/o man	Nodal	AML	Day 473
	55 y/o woman	Splenic	MDS	Day 552
	60 y/o man	Splenic	AML	Day 1173
	72 y/o man	Nodal	BCC and SCC	Day 213
	75 y/o man	Nodal	BCC, SCC, and sebaceous carcinoma	Day 99
	67 y/o	Nodal	Squamous cell carcinoma of the skin	Day 1024
	71 y/o man	Nodal	Bowen's disease	Day 108
	71 y/o man	Splenic	Meningioma	Day 18

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma

Brief narratives for each of the patients in table 47 are provided:

1. SUBJID (b) (6) :

50 y/o woman with stage 4 nodal MZL diagnosed in 2015, s/p multiple treatments including ASCT (b) (6) with progressive disease (b) (6), s/p bridging RCHOP 7/2023 and zanubrutinib 9/2023-10/2023, course complicated by neutropenic colitis, s/p lymphodepleting chemotherapy 10/2023 and liso-cel administration (b) (6) , died from a T cell lymphoma on day 32. The patient presented with two new splenic lesions on CT on day 22 retrospectively diagnosed as a grade 4 T-cell lymphoma based on autopsy findings. Followup PET on D29 showed uptake in the bone marrow, spleen, and liver. The histopathology report revealed a diffuse infiltration within the mesenteric and aortic lymph nodes, resulting in effacement of the lymph node architecture and extracapsular extension. Necrosis was evident. The cells had marked atypia with spindle cell morphology and hyperchromatic nuclei along with dense eosinophilic cytoplasm. There were also atypical cells identified in liver sections. Immunohistochemistry on a lymph node and liver block showed diffuse positivity for CD45. Interpretation of stains was challenging due to tissue autolysis, but a proportion of cells on a lymph node and liver block were positive for CD4, CD3, CD5, CD30, and bF1. CD2 and CD8 positive T cells were identified. The investigator concluded a probable de-novo development of a T cell lymphoma extensively involving the liver. DNA-based droplet digital PCR detected 33, 927 copies/microgram in the liver and 12, 377 copies/microgram in the aortic lymph node versus 51, 6000 copies/microgram in the peripheral blood. Insertion site analysis conducted on the liver and aortic lymph node samples revealed that the CAR+ cell population was polyclonal.

2. SUBJID (b) (6)

57 y/o man with stage 4 nodal MZL diagnosed with AML on day 473 and died on day 490. Post-CAR-T infusion course was otherwise remarkable for grade 3 prolonged thrombocytopenia diagnosed on day 23 which improved to grade 2 by day 94.

Thrombocytopenia persisted through day 360 (platelet count 55K). No autopsy was performed.

3. SUBJID (b) (6)
55 y/o woman with stage 4 splenic MZL diagnosed October 2017, s/p multiple therapies including bridging bendamustine and obinutuzumab November 2021, with day 552 diagnosis of grade 4 myelodysplastic syndrome with D775 death due to pneumonia. Day 542 bone marrow biopsy was notable for megakaryocytic dysplasia and cytogenetics with 7Q31 deletion and indeterminate RNAscope in-situ hybridization for the transgene. Patient received decitabine and cedazuridine for her MDS. Bone marrow biopsy for lymphoma was negative on day 600.

4. SUBJID (b) (6) :
60 y/o male with stage 3 splenic MZL, diagnosed with grade 3 AML on study day 1056. Bone marrow biopsy flow cytometry showed 9.4% blasts (CD34+, CD117WK, CD33+, HLADRWK, CD15+, CD56+, CD38+, MPO+). FLT3 ITD, ASXL1, and TP53 mutated disease was found. 60% involvement by CD34+ blasts on bone marrow biopsy. Patient received cytarabine and gilteritinib. Bone marrow biopsy was received for transgene testing but test result was pending at time of database lock for report. Subject was negative for RCL within first year after liso-cel infusion.

5. SUBJID (b) (6)
72 y/o male stage 4 nodal MZL initially diagnosed in 2007 with multiple skin cancers as below. Three basal cell carcinoma (BCC) tumor samples and five squamous cell carcinoma (SCC) tumor samples were tested for presence of transgene by RNAscope in-situ hybridization. 6 samples were negative for the transgene (3 BCC and 3 SCC) and 2 (2 SCC) were unevaluable due to no tumor cells in the tissue).
- day 213 grade 2 squamous cell carcinoma of the skin, s/p MOHS micrographic skin surgery on the left scalp
- day 294 grade 2 squamous cell carcinoma of skin (left hand) whose management is unclear as on the same day the patient had “bone debridement with electrodessication and cautery to subcutaneous fat to remove a lesion suspected to be squamous cell carcinoma”
- day 522 grade 2 squamous cell carcinoma of the skin (left medial leg), s/p excision of left hand squamous cell carcinoma via biopsy and s/p MOHS micrographic skin surgery on the left leg
- day 701 grade 2 squamous cell carcinoma of skin (left temple) s/p MOHS micrographic skin surgery on day 731
- day 701 basal cell carcinoma (left sacrum), and basal cell carcinoma (right lateral forehead) s/p MOHS micrographic skin surgery
- day 904 grade 2 squamous cell carcinoma (right dorsal hand) resolved on day 939 (unclear how it resolved)
- day 939 grade 2 basal cell carcinoma (left neck) resolved on the same day (unclear how it resolved)

6. SUBJID (b) (6)
75 y/o male with stage IV nodal MZL diagnosed in 2021 with multiple skin cancers as below. There were no tumor samples available from the 4 basal cell carcinomas, 2 squamous cell carcinomas, and 1 sebaceous carcinoma for transgene testing. The subject was negative for replication-competent lentivirus on blood sample of 1 basal cell carcinoma within the first year after liso-cel infusion but not for 3 basal cell carcinomas, 2 squamous cell carcinomas, and one sebaceous carcinoma.
- day 99 grade 2 basal cell carcinoma (right temple), s/p MOHS micrographic skin surgery on day 197
- day 246 grade 2 squamous cell carcinoma (right posterior dorsum of hand), s/p MOHS micrographic skin surgery on day 269
- day 304 grade 2 squamous cell carcinoma (right chest), s/p MOHS micrographic skin surgery on day 337
- day 409 grade 2 basal cell carcinoma (nose), s/p MOHS micrographic skin surgery on day 484
- day 484 grade 2 basal cell carcinoma (left cheek and nose), s/p MOHS micrographic skin surgery day 561 (left cheek) and day 575 (nose)
- day 564 grade 2 sebaceous carcinoma (right cheek and forehead), s/p MOHS micrographic skin surgery day 575

7. SUBJID (b) (6)
67 y/o female with stage IV nodal MZL with PMH significant for squamous cell carcinoma of the skin in 2007, diagnosed with grade 2 squamous cell carcinoma of the scalp on day 1024 in the setting of a new onset autoimmune systemic disease process that began on day 183.

8. SUBJID (b) (6)
71 y/o male with stage IV nodal MZL diagnosed with grade 2 Bowen's disease (right back on day 108), s/p excisional biopsy on day 108.

9. SUBJID (b) (6) :
71 y/o male with stage 4 splenic MZL incidentally diagnosed with a 1.5 cm left frontal meningioma on MRI brain on day 18 during workup for investigator-identified neurotoxicity.

Autoimmune Disorders

The Applicant's Position:

No autoimmune disorders were reported (Table 17) during the treatment-emergent period or post treatment-emergent period for 3L+ MZL subjects in Study FOL-001.

The FDA's Assessment:

The FDA disagrees with the Applicant's assessment and notes one patient with autoimmune complications following treatment with liso-cel. Patient USUBJID (b) (6) was a 67 y/o woman with stage IV nodal MZL, who died on day 1058 of Klebsiella

pneumonia while on a JAK inhibitor in the setting of an autoimmune process involving the skin, joints, eyes, liver, and lungs. On day 177 following liso-cel infusion, the patient had a skin biopsy consistent with a grade 2 granuloma. On day 183, the patient developed dermatitis on her back and arms, new joint stiffness, scleritis, and abnormal liver function tests. Symptoms were reportedly refractory to topical steroids, sulfasalazine, and hydroxychloroquine. On day 357, the patient developed a disseminated papular rash on her trunk and extremities with some improvement on hydroxychloroquine. Day 414 skin biopsy confirmed the presence of a granulomatous dermatitis. A skin biopsy on day 457 was sent for EGFR staining to assess for a relationship to CAR cells and was negative. Interstitial granulomatous dermatitis was diagnosed day 487 in the setting of symptoms of polyarthralgia and scleritis for which the patient received sulfasalazine and prednisolone eye drops. Liver function test abnormalities were noted on day 520, and tofacitinib was initiated on day 723 with improvements in the skin, joints, eyes, and ultimately LFTs. When tofacitinib was discontinued in January 2024 for thrombocytopenia, patient's skin, eye, and joint symptoms rapidly progressed with new lung nodule formation developing in February 2024. Widespread centrilobular nodules were noted on day 919 for which Upadacitinib was started following a diagnosis of grade 2 squamous cell carcinoma on day 1024. The patient ultimately died from Klebsiella pneumonia on day 1058 in the setting of JAK inhibitor use but, more importantly, in the setting of systemic autoimmune disease for which the JAK inhibitor was prescribed.

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:
The FDA agrees with the Applicant's assessment.
[FDA will complete this section.]

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:
The FDA agrees with the Applicant's assessment.
[FDA will complete this section.]

Laboratory Findings

Table 4848: Applicant - Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Subjects Treated with Liso-cel in Study FOL-001

Laboratory Abnormality	Grade 3 or 4 (%)
Lymphocyte count decreased	66 (98.5)
Neutrophil count decreased	56 (83.6)
White blood cell decreased	56 (83.6)
Platelet count decreased	19 (28.4)
Anemia	17 (25.4)
Fibrinogen decreased	6 (10.0)

Source: ISS - ADLBLDC, ISS - ADLBSLDC

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 67 MZL subjects who were treated with lisocel. The evaluable number for each lab, rather than the total number of safety population, were used as denominator during calculation of frequencies. The evaluable population for each lab included subjects with a baseline and at least one post treatment value. Baseline lab values were assessed prior to lymphodepleting chemotherapy.

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. The treatment emergent window included abnormal lab value upto 90 days post treatment with lisocel.

The table below summarizes treatment emergent laboratory abnormalities:

Table 49 49: FDA - Laboratory Abnormalities Occurring in ≥ 10% of MZL Subjects Treated with Liso-cel in Study FOL-001

PARAMCD_FDA	Evaluable N	All grade, N	All grade, %	Grade 3 and 4, N	Grade 3 and 4, %
Lymphocyte decreased	67	66	99%	66	99%
WBC decreased	67	65	97%	56	84%
Neutrophil decreased	67	61	91%	56	84%
Hemoglobin decreased	67	55	82%	17	25%
Platelet decreased	67	51	76%	19	28%
Calcium decreased	67	41	61%	5	7%

Albumin decreased	67	38	57%	1	1%
ALT increased	66	37	56%	5	8%
AST increased	66	34	52%	5	8%
Fibrinogen decreased	60	29	48%	6	10%
Bilirubin increased	65	25	38%	1	2%
Creatinine increased	67	23	34%	1	1%
Sodium decreased	67	23	34%	2	3%
Potassium decreased	67	21	31%	3	4%
ALP increased	67	20	30%	1	1%
Magnesium decreased	64	14	22%	1	2%
APTT increased	62	13	21%	1	2%
Source: FDA Analysis of ADLB data, study FOL-001; and data confirmed during labeling negotiation. N number, WBC white blood cells, ALT alanine aminotransferase, AST aspartate aminotransferase, ALP alkaline phosphatase, APTT activated partial thromboplastin time					

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 the Applicant's assessment.

Electrocardiograms (ECGs)

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

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

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 March 31, 2025 was submitted on August 6, 2025. The new data cutoff date provides an additional 4 months of followup compared to the primary data cutoff used for the Study FOL-001 (November 29, 2024). As of the November data cutoff date, the 3L+ MZL cohort had completed enrollment. The median on study followup time increased from 24.08 months to 26.32 months with

the new data cutoff date. The TEAE, grade >3 TEAE, SAE, grade 5 AE, and AESI types and frequencies remained the same with no additional TEAEs reported. Two subjects discontinued the study due to death for the following reasons:

- USUBJID (b) (6) : 60 y/o man; progressive refractory AML at day 1173 previously diagnosed at day 1056.
- USUBJID (b) (6) 60 y/o woman; septic shock at day 584

No new MZL subject was infused with liso-cel.

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 in subjects with 3L+ MZL.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.
[FDA will complete this section.]

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 3L+ MZL Study 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.

The FDA's Assessment:
There was limited representation of patients with extranodal MZL and splenic MZL. The small sample sizes make it challenging to make any conclusions about differences between subgroups.

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-Applicanted, or company alliance partner-Applicanted 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 were integrated with respective parent study in the ISS, per the ISS SAP.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

[FDA will complete this section.]

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 = 13; 3L+ MZL Cohort 4):

- TEAEs occurred in all 13 (100%) subjects, 12 (92.3%) experienced Grade ≥ 3 TEAEs, and 10 (76.9%) subjects experienced serious TEAEs (ADSL, ADCORE, ADAE, ADAES).
- AESI occurred in 10 (76.9%) subjects, most commonly, CRS (10 [76.9 %] subjects) and prolonged cytopenia (7 [53.8 %] subjects) (ADSL, ADCORE, ADAE, ADCRSNT, ADCPT).
  - CRS
    - No subjects experienced Grade ≥ 3 CRS (ADSL, ADCORE, ADAE, ADCRSNT, ADAES, ADAETTE).
    - The median time to first onset of CRS was 7.0 (range: 2 to 29) days.
    - CRS resolved in all subjects, and the median time to resolution was 4.0 (range: 2 to 8) days.
  - iiNT
    - No subjects experienced Grade ≥ 3 iiNT (ADSL, ADCORE, ADAE, ADCRSNT, ADAES, ADAETTE).
    - The median time to iiNT onset was 6.0 (range: 5 to 36) days.
    - iiNT resolved in all subjects, and the median time to resolution was 9.5 (range: 1 to 18) days.

Pooled Analyses

Data:

Table 5050: Applicant - Overall Summary of Safety in Pooled Studies

	Number (%) Subjects					
Safety Parameter	**3L+ MZL FOL-001 Cohort 4 N = 67**	**3L+ MCL N = 88**	**3L+ FL FOL-001 Cohorts 1, 2 N = 107**	**3L+ CLL/SLL N = 117**	**2L/3L+ LBCL Total N = 582**	**Overall Total N = 961**
Liso-cel-treated Analysis Set						
Deaths Occurred After First Liso-cel Infusion	9 (13.4)	46 (52.3)	11 (10.3)	44 (37.6)	234 (40.2)	344 (35.8)
Primary Cause of Death						
PD	4 (6.0)	29 (33.0)	6 (5.6)	27 (23.1)	184 (31.6)	250 (26.0)
AE	1 (1.5)	5 (5.7)	2 (1.9)	5 (4.3)	23 (4.0)	36 (3.7)
COVID-19	0	7 (8.0)	2 (1.9)	6 (5.1)	8 (1.4)	23 (2.4)
Unknown	0	1 (1.1)	0	0	7 (1.2)	8 (0.8)
Other	4 (6.0)	4 (4.5)	1 (0.9)	6 (5.1)	12 (2.1)	27 (2.8)
Subjects with any TEAE	67 (100.0)	88 (100.0)	105 (98.1)	117 (100.0)	575 (98.8)	952 (99.1)
Any Grade ≥ 3	59 (88.1)	76 (86.4)	83 (77.6)	108 (92.3)	475 (81.6)	801 (83.4)
Any Grade 5	2 (3.0)	4 (4.5)	0	5 (4.3)	16 (2.7)	27 (2.8)
Any Serious	26 (38.8)	47 (53.4)	28 (26.2)	72 (61.5)	250 (43.0)	423 (44.0)
Liso-cel-related	63 (94.0)	77 (87.5)	95 (88.8)	112 (95.7)	473 (81.3)	820 (85.3)
Liso-cel-related Grade ≥ 3	44 (65.7)	43 (48.9)	64 (59.8)	77 (65.8)	279 (47.9)	507 (52.8)
Liso-cel-related Grade 5	2 (3.0)	3 (3.4)	0	1 (0.9)	11 (1.9)	17 (1.8)
Liso-cel-related Serious	20 (29.9)	34 (38.6)	22 (20.6)	58 (49.6)	177 (30.4)	311 (32.4)
LDC-related	54 (80.6)	74 (84.1)	78 (72.9)	106 (90.6)	476 (81.8)	788 (82.0)
Subjects with any treatment-emergent AESI						
CRS	51 (76.1)	54 (61.4)	63 (58.9)	99 (84.6)	255 (43.8)	522 (54.3)
Grade 1-2	48 (71.6)	53 (60.2)	62 (57.9)	89 (76.1)	240 (41.2)	492 (51.2)
Grade 3-4	3 (4.5)	1 (1.1)	1 (0.9)	10 (8.5)	14 (2.4)	29 (3.0)
iiNT	22 (32.8)	27 (30.7)	16 (15.0)	53 (45.3)	173 (29.7)	291 (30.3)
Grade 1-2	19 (28.4)	19 (21.6)	14 (13.1)	31 (26.5)	117 (20.1)	200 (20.8)
Grade 3-4	3 (4.5)	8 (9.1)	2 (1.9)	22 (18.8)	53 (9.1)	88 (9.2)
IRR	0	2 (2.3)	0	0	4 (0.7)	6 (0.6)

Table 5050: Applicant - Overall Summary of Safety in Pooled Studies

	Number (%) Subjects					
Safety Parameter	**3L+ MZL FOL-001 Cohort 4 N = 67**	**3L+ MCL N = 88**	**3L+ FL FOL-001 Cohorts 1, 2 N = 107**	**3L+ CLL/SLL N = 117**	**2L/3L+ LBCL Total N = 582**	**Overall Total N = 961**
MAS	3 (4.5)	0	0	4 (3.4)	4 (0.7)	11 (1.1)
TLS	1 (1.5)	2 (2.3)	0	13 (11.1)	2 (0.3)	18 (1.9)
Grade ≥ 3 infections	6 (9.0)	13 (14.8)	7 (6.5)	20 (17.1)	69 (11.9)	115 (12.0)
Prolonged cytopenia	28 (41.8)	35 (39.8)	26 (24.3)	63 (53.8)	209 (35.9)	361 (37.6)
Hypogammaglobulinemia	1 (1.5)	6 (6.8)	4 (3.7)	15 (12.8)	64 (11.0)	90 (9.4)
SPM	1 (1.5)	3 (3.4)	1 (0.9)	2 (1.7)	8 (1.4)	15 (1.6)
Autoimmune disorders	0	0	0	0	1 (0.2)	1 (0.1)

The 2L/3L+ LBCL population includes 3L+ LBCL subjects from studies 017001 (DLBCL Cohort; n = 268, BCM-001 (Cohorts 1, 3, and 7; n = 55), and 017007 (n = 82), and 2L LBCL subjects from studies BCM-003 Arm B (n = 89), 017006 (n = 61) and BCM-001 (Cohort 2; n = 27).
Prolonged cytopenia includes subjects who had treatment-emergent (ie, worsens by ≥ 1 grade compared to baseline) Grade 3 or 4 lab abnormalities of decreased hemoglobin, absolute neutrophil count, or platelet count at Day 30 (+/- 2 days) after liso-cel infusion in Study 017004, Day 35 (+/- 6 days) after liso-cel infusion for BCM-003 and at Day 29 (+/- 2 days) after liso-cel infusion in other studies.
Source: ISS - ADSL, ISS - ADAE, ISS - ADSAFSUM

The Applicant's Position:
The safety profile of liso-cel in the MZL population was manageable and consistent with previously reported safety findings with liso-cel in MCL, FL, CLL/SLL, and LBCL with no new safety signals or new types of clinically important events identified (Table 22).

The FDA's Assessment:
The FDA performed a pooled safety data analysis as summarized below. No new safety signals were identified.

The integrated safety analysis included adverse reaction analysis from a total of 961. patients with various histologies treated with liso-cel.

Table 51. FDA - FDA Integrated Safety Analysis of Liso-cel

STUDY ID	LBCL	CLL	SLL	MCL	FL	MZL	Overall
017001	268	-	-	88	-	-	356
017004	-	108	9	-	-	-	117
017006	61	-	-	-	-	-	61
017007	82	-	-	-	-	-	82
JCAR017-BCM-001	82	-	-	-	-	-	82
JCAR017-BCM-003	89	-	-	-	-	-	89
JCARFOL-001	-	-	-	-	107	67	174
Total	582	108	9	88	107	67	961

Source: FDA Analysis of ISS ADSL dataset
Abbreviations: LBCL, large B cell lymphoma; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

Table 52. FDA - FDA Baseline Demographics of Pooled Safety Population (n=961)

Parameter	Integrated Safety Population N= 961 n (%)
Age	
Median	65 (18-86)
Age < 65	476 (49.5)
Age ≥ 65-75	377 (39.2)
Age >75	108 (11.2)
Sex	
Male	611 (63.6)
Female	350 (36.4)
Race	
White	735 (76.5)
Asian	58 (6)
Black	32 (3.3)
Native Hawaiian	2 (0.2)

American Indian	2 (0.2)
Others/not reported	58 (6)
Unknown	57 (5.9)
Other	2 (0.2)
Multiple	1 (0.1)
No entry	14 (1.5)
Region	
N America	743 (97.6)
US	735 (96.6)
Canada	8 (0.83)
Europe	190 (19.8)
Japan	28 (2.9)

Table 53. FDA - FDA summary of TEAE >3% in the Integrated Analysis Set (n=961)

Dictionary Derived Term	MZL (N=67) All Grade (%)	MZL (N=67) ≥ G3 (%)	FL (N=107) All Grade (%)	FL (N=107) ≥ G3 (%)	CLL/SLL (N=117) All Grade (%)	CLL/SLL (N=117) ≥ G3 (%)	MCL (N=88) All Grade (%)	MCL (N=88) ≥ G3 (%)	LBCL (N=582) All Grade (%)	LBCL (N=582) ≥ G3 (%)
CRS	76.1	4.48	58.9	0.93	84.6	8.55	61.4	1.1	43.8	2.58
Diarrhea	28.4	1.49	14.94	-	29.1	0.85	17.1	-	21.7	0.86
Fatigue	22.4	1.49	11.21	-	34.2	5.98	35.2	1.1	34	1.03
Headache	20.9	1.49	28	-	29.1	0.85	22.7	-	25.6	1.37
Tremor	19.4	-	14.95	-	23.9	1.71	11.4	-	13.4	0.69
Nausea	17.9	1.49	9.35	-	33.3	-	18.2	2.3	26.8	1.03
Dizziness	11.9		2.8	-	24.8	-	6.8	-	16.8	0.34
Decreased appetite	10.5	2.99	5.61	-	24.8	3.42	20.5	4.6	20.6	2.06
Hypotension	10.5	-	8.41	-	17.95	0.85	12.5	-	15.4	2.41
Pyrexia	10.5	-	19.6	-	27.4	0.85	17.1	-	19.2	-
Aphasia	8.96	-	6.54	0.93	9.4	2.56	4.6	-	6.01	1.89
Confusional state	8.96	1.49	2.8	0.93	26.5	9.4	15.9	2.3	11	1.89
Insomnia	8.96	-	4.67	-	17.1	0.85	12.5	-	11.3	0.17
Pleural effusion	8.96	2.99	0*	-	2.56	0.85	4.6	-	4.5	0.86
Vomiting	8.96	-	3.74	-	13.7	-	5.68	-	14.4	0.17
Abdominal pain	7.46	-	3.74	-	17.95	-	7.95	2.3	11.9	1.55
Back pain	7.46	-	4.67	--	12.8	0.85	14.8	1.1	9.97	0.52
Chills	7.46	-	3.74	-	18.8	0.85	11.4	-	7.56	-
Fall	7.46	-	0*	-	6.8	-	3.4	1.1	3.78	0.52
Arthralgia	5.97	-	8.41	-	10.3	-	11.4	-	10.65	0.69
Asthenia	5.97	1.49	13.08	-	9.4	-	1.1	-	8.08	1.2
Dehydration	5.97	-	0*	-	4.27	-	4.6	1.1	5.67	0.69
Disorientation	5.97	1.49	1.87	-	-	-	-	-	1.2	0.34
Dyspnea	5.97	-	0.93	-	17.95	5.13	9.1	-	9.62	0.69
Hypertension	5.97	2.99	4.67	0.93	11.11	5.98	10.2	3.4	9.62	3.44
Neck pain	5.97	-	1.87		7.69	-	3.4	-	3.78	0.52
Peripheral edema	5.97	-	3.74		-	-	-	-	13.06	0.52
Anxiety	4.48	-	1.87		13.68	0.85	12.5	1.1	6.87	0.17
Bone pain	4.48	-	1.87	-	3.42	-	3.4	-	4.64	0.17
Cognitive disorder	4.48	-	0.93	-	2.56	0.85	-	-	2.23	0.52

Cough	4.48	-	6.54	-	16.24	-	-	-	15.1	-
COVID-19	4.48	1.49	0.93	0.93	-	-	1.1	1.1	1.2	0.69
Dry skin	4.48	-	0.93	-	5.1	-	1.1	-	2.4	-
HLH	4.48	4.48	0*	-	3.42	2.56	-	-	-	0.52
Hypervolemia	4.48	-	-	-	5.1	0.85	2.3	-	-	0.17
Hypoxia	4.48	-	1.87	0.93	13.7	10.26	3.4	1.1	3.26	1.03
Non-cardiac chest pain	4.48	-	2.8	-	7.69	-	-	-	2.92	0.34
Pain in extremity	4.48	-	2.8	-	6.84	0.85	10.2	1.1	7.22	0.69
Presyncope	4.48	-	-	-	0.85	-	-	-	1.03	-
Sinus tachycardia	4.48	-	0.93	-	11.11	0.85	5.7	-	9.45	-
Weight decreased	4.48	-	0.93	-	5.98	-	3.4	-	4.98	0.86

Abbreviations: MZL, marginal zone lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; LBCL, large B cell lymphoma

[FDA will complete this section.]

Human Carcinogenicity or Tumor Development

The Applicant's Position:
There have been 8 subjects with malignancies reported including 1 T-cell malignancy in the 3L+ MZL Liso-cel-treated Analysis Set. No vector-mediated malignancies have been identified to date.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.
[FDA will complete this section.]

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 protocol.

The FDA's Assessment:
FDA agrees with the Applicant's assessment

Pediatrics and Assessment of Effects on Growth (If applicable)

The Applicant's Position: Not applicable

The FDA's Assessment:
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 (PAS to remove REMS under FDA review), 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 CA082-1205 is proposed to characterize long-term efficacy and safety (including the risk of secondary malignancies) after liso-cel treatment in 3L+ R/R MZL patients. This study will be in the real-world setting, based on secondary data that are collected from one or more existing independent registries.

Per the REMS Modification Notification Letter dated 07-Mar-2025, REMS is no longer required for Breyanzi. Thus, the identified and potential risks of liso-cel are adequately addressed in the current product labeling including the medication guide, and no additional risk-minimization measures are considered necessary at this time.

The FDA's Assessment:
FDA agrees with the Applicant.
[FDA will complete this section.]

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.

Therefore, a separate LTFU for safety with active surveillance in the R/R MZL patient population after treatment with liso-cel will be required. The Applicant has proposed to conduct Study XXX 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 67 3L+ MZL subjects treated with liso-cel with a median study follow-up of 24.08 months demonstrated a well-tolerated and manageable safety profile, which is consistent with that previously reported for the approved indications in the ISS table included in this sBLA application.

- No new safety signals or new types of clinically important events were identified with liso-cel monotherapy in 3L+ MZL (Study FOL-001, Cohort 4).
- The safety events were consistent with previously reported safety findings with liso-cel monotherapy in MCL, FL, CLL/SLL, and LBCL (Table 22).
- 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 and iiNT were 4.5% each, and that of MAS/HLH and hypogammaglobulinemia were 4.5% and 1.5%, respectively, which were considered manageable using the protocol management guidance and standard of care.
- The rates of Grade ≥ 3 infections (9.0%) and prolonged cytopenia (41.8%) were considered manageable.

The FDA's Assessment:
[FDA will complete this section.]

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 relapsed or refractory FL or MZL. The Applicant submitted clinical data from cohort 4 consisting of subjects with relapsed or refractory MZL. The primary endpoint was ORR, defined as the percentage of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) up to 60 months after JCAR017 infusion per Lugano criteria and as determined by an independent review committee (IRC).
Per statistical analysis plan (SAP), the hypothesis testing was planned for each cohort in hierarchical manner to control for type 1 error with testing for ORR followed by CRR. Per Applicant, with a planned sample size of 60 3L+ MZL patients (cohort 4), using a 1-sided 0.025 significance level, the study would have a 90% power to detect an ORR of 72% versus a null rate of 50%, or a CRR of 19% versus a null CRR rate of 5%.
In support of these assumptions, the SAP cites following data from the literature:

> "Ibrutinib data (n=63), 3L+ subjects, assessed by CT: ORR 48%, CRR 3%, median DOR not reached, median PFS 14 months; 2 median prior lines of therapy (Noy, 2017)." (Source: SAP, JCAR-FOL-001 study)

It should be noted that the statistical testing is descriptive, and these are just estimates to inform the sample size and the ability to rule out a null rate.

8.4. Conclusions and Recommendations

The FDA's Assessment:
The benefit-risk assessment of liso-cel for treatment of adults with relapsed refractory MZL after two or more prior lines of systemic therapy is favorable.

Efficacy:
Study JCAR-FOL-001 MZL provides substantial evidence of effectiveness of the liso-cel for the treatment of adults with relapsed refractory MZL after two or more prior lines of systemic therapy.
JCAR-FOL-001 was a global, open-label, phase 2, single arm trial which enrolled 77 patients with relapsed or refractory marginal zone lymphoma who received at least two prior therapies (including at least one line of combination systemic therapy or therapy with an anti-CD20 antibody and an alkylating agent) or patients who have relapsed after HSCT. An indication for systemic treatment was not required for study enrollment and was per investigator assessment.

Patients received fludarabine 30 mg/m2/day and cyclophosphamide 300 mg/m2/day lymphodepleting chemotherapy for 3 days prior to lisocabtagene maraleucel infusion on day 1 at a dose of 100 X 10^{-6} CAR-positive T cells. Efficacy was established on the basis of overall response rate (ORR) as assessed by CT using the Lugano Classification (Cheson 2014).

Among 77 subjects with relapsed or refractory MZL who underwent leukapheresis, the ORR was 84.4% (95% CI: 74.4, 91.7) with a CR rate of 55.8% (95% CI: 44.1, 67.2). In 66 patients who were treated with intended dose of conforming liso-cel and had sufficient follow up for duration of response, the ORR was 95.5% (95% confidence interval [CI]: 87.29, 99.05) with a CR rate of 62.1% (95% CI: 49.3, 73.8). With an estimated median follow up from date of first response of 21.59 months (95% confidence interval [CI]: 17.28, 22.77), the median duration of response was not reached (95% confidence interval [CI]: 25.59, NR). The one year and two year rates of continued remission were 96.7 (95% confidence interval [CI] 87.3, 99.2) and 90.1 [95% confidence interval [CI] 73.1, 96.6)

Safety:
The safety profile of lisocabtagene maraleucel was supported by an analysis of 67 patients with relapsed or refractory MZL treated with liso-cel. The most common adverse events (>20%) were cytokine release syndrome, fatigue, diarrhea, musculoskeletal pain, headache, and tremor. The most common grade 3 to 4 laboratory abnormalities (>10%) were: lymphocyte count decreased, neutrophil decreased, white blood count decreased, platelet count decreased, hemoglobin decreased and fibrinogen decreased.
Serious adverse events occurred in 39% of patients, most often due to cytokine release syndrome (19.4%), neurotoxicity (14.9%), encephalopathy (10.45%), aphasia (7.46%),

tremor (4.5%), sepsis (4.5%), and 3% each of dizziness, transient ischemic attack, and infusion related hypersensitivity. Adverse events of special interest included the following: cytokine release syndrome (76%), investigator-identified neurotoxicity (33%), infusion related hypersensitivity reaction (1.5%); hemophagocytic lymphohistiocytosis (4.5%); tumor lysis syndrome (1.5%); hypogammaglobulinemia ( ); grade 3 and greater infections (9%); second primary malignancies (12%); and prolonged cytopenias in 97% (65/67) patients i.e. had any grade decreased hemoglobin, platelet or neutrophil count at day 29 day visit (+/-2 window). Grade 3 or higher prolonged cytopenias persisted in 40% (27/67) patients, including thrombocytopenia in 21%, neutropenia in 27% and anemia in 9% of patients.

Benefit-Risk:
The benefit-risk assessment of liso-cel for treatment of adults with relapsed refractory MZL after two or more prior lines of systemic therapy is favorable.

The safety profile was consistent with other lymphomas, and no new safety signal of concern was identified. Given the risk of secondary malignancies and the long-term safety, a 15-year prospective observational post-marketing safety study (Study CA082-1205) including at least 300 adult patients with relapsed or refractory marginal zone lymphoma will be required.
The ORR of 95.5% observed in FOL-001 far exceeds the ORRs seen with available therapies for this disease which range from 51-74% for therapies with regular approval. The CR rate of 62.1% observed in FOL-001 also far exceeds the CRR seen with approved products (13-29%). The high and durable ORR further supported by high complete response rate. This denotes clinical benefit in this relapsed refractory MZL patients who have failed 2 or more prior lines of therapy and therefore supports a traditional approval.

Recommendation on Regulatory Actions

The clinical review team recommends traditional approval of liso-cel for the treatment of adult patients with R/R MZL who have received at least 2 prior lines of systemic therapy. The basis for the recommendation is the large magnitude of ORR and its durability, in the context of a high CRR and an acceptable safety profile. In this relapsed refractory MZL population after 2 or more prior lines of systemic therapy, the review team considers this treatment effect to be clinically meaningful and to represent clinical benefit. The overall risks of liso-cel in the indicated population are comparable to approved indications and are adequately mitigated through product labeling. As with prior approvals, a PMR study to follow at least 300 patients with MZL treated with the commercial product for short term and long-term toxicity was requested and agreed upon.

X

Primary Clinical Reviewer

X

Clinical Pharmacology Reviewer

X

OCE MORE Team Lead

X

CBER MHB Clinical Team Lead

X

Associate Director of Labeling

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

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

The Applicant's Position:
Not applicable. Liso-cel was granted ODD, for treatment of nodal MZL (US ODD # DRU-2023-9337, 30-Mar-2023), extranodal MZL (US ODD # DRU-2023-9338, 17-Apr-2023), and splenic MZL (US ODD # DRU-2023-9336, 17-Apr-2023). Per PREA and 21 CFR 314.55 (d), liso-cel is exempt from pediatric study requirements for these three subtypes of MZL.

The FDA's Assessment:

FDA agrees with Applicant's assessment. Study JCAR017-FOL-001 MZL cohort did not enroll or treat pediatric patients. This is a supplemental BLA application seeking registration of lisocel for the indication of adults with r/r MZL after two or more prior lines of systemic therapy. Lisocel has orphan drug designation for treatment of MZL. Therefore, the application is exempt from Pediatric Research Equity Act (PREA) requirements for this indication.

11 Labeling Recommendations

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

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Section 1: Indications and Usage	BREYANZI is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least two prior lines of systemic therapy.	The proposed indication was acceptable.
Section 2: Dosage and Administration	For MZL the dose is 90 to 110 × 10^6 CAR-positive viable T cells	The proposed dose was acceptable.
Section 5: Warnings and Precautions	• CRS (5.1) • Neurologic toxicities (5.2) • Serious infections (5.4) • Prolonged cytopenias (5.5) • Hypogammaglobulinemia (5.6)	The safety data in section 5 was updated based on internal review and adjudication.

Section 6: Adverse Reactions Clinical Trials Experience (TRANSCEND FL-MZL Cohort)	Section 6.1: Clinical Trials Experience The most common nonlaboratory adverse reactions (≥ 20%) in MZL are CRS, diarrhea, fatigue, musculoskeletal pain, and headache. The most common Grade 3-4 laboratory abnormalities (≥ 10%) include lymphocyte count decreased, neutrophil count decreased, white blood cell decreased, platelet count decreased, hemoglobin decreased, and fibrinogen decreased. Section 6.2: Postmarketing Experience	The information in this section was revised to describe safety database and BREYANZI exposure based on the current labeling practice. Study names (e.g., TRANSFORM, TRANSCEND) were replaced with Study numbers as the names were considered promotional. Footnotes were grouped as multiple related terms for brevity and to reduce visual clutter. Blindness was added to section 6.2 based on adverse reactions identified during postmarketing use of the product, where the evidence supports a reasonable possibility of causal association.
Section 8.5 Geriatric Use	In patients with MZL, 30 (45%) of 67 patients were 65 years of age or older, and 10 (15%) were 75 years of age or older. No clinically important differences in safety or effectiveness of BREYANZI were observed between patients aged ≥ 65 and younger patients.	Proposed changes were acceptable.
Section 12: Clinical Pharmacology	• Pharmacokinetics (12.3) • Immunogenicity (12.6)	Section 12.6 was revised based on the FDA guidance on presenting immunogenicity data in product labeling.
Section 14 Clinical studies	Addition of TRANSCEND-FL clinical study (3L+ MZL Cohort 4).	Section was revised to describe the study design, patient eligibility, intervention, patient demographics and characteristics, endpoints, and significant results based on current labeling practice. To maintain intra-label consistency, the efficacy data on both BREAYNZI-treated and All Leukopheresed patients were included in Table 29. Similarly, DOR data in only BREYANZI-treated patients was included in Table 30.
Boxed Warning, 2.3 Management of Severe Adverse Reactions (Monitoring) and 5.	Prescribing Information has been updated to remove REMS information from BREYANZI label per the FDA	Proposed changes were acceptable.

Warnings and Precautions (5.1 CRS, 5.2 NT, 5.3 BREYANZI REMS) and 17 (Patient Counseling Information).	REMS Modification Notification Letter dated 07-Mar-2025.	

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team determined that a REMS was not required to ensure safe and effective use of liso-cel for the indicated population. The review team made this determination given the consistency of the safety profile with approved CAR T cell therapies for other lymphomas, and the established management guidelines and extensive experience of the medical hematology/oncology community in managing immune-mediated adverse reactions, including those associated with CAR T therapies like liso-cel. It should also be noted that the REMS requirement for currently approved CAR T cell therapies for hematological malignancies was eliminated in June 2025. Recommendations for the safe and effective use of liso-cel, including monitoring for immune-related adverse events, are provided in the USPI as well as in the patient medication guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The pharmacovigilance plan (PVP) includes a long-term, prospective, non-interventional PMR registry study in patients with MZL treated with liso-cel. The Applicant will complete a post-marketing, prospective, multi-center, observational study to assess and characterize the risk of secondary malignancies and the long-term safety following treatment with liso-cel (Study CA082-1205). The study will include at least 300 adult patients with relapsed or refractory marginal zone lymphoma; each enrolled patient will be followed for 15 years after product administration.

The Applicant will conduct this study according to the following schedule:
Protocol Submission: March 31, 2026
Study Completion Date: March 31, 2048
Final Report of Study Results: March 31, 2049

14 Chief, Malignant Hematology Branch

The Malignant Hematology Branch (MHB) concurs with the primary clinical review team and the Oncology Center of Excellence's recommendation to grant a traditional approval to lisocabtagene maraleucel (Breyanzi) fot the the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) after two or more lines of systemic therapy.

X

Upendra Mahat, MD
Branch Chief, Malignant Hematology Branch, DCEH/OCE/OTP/CBER

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 (DCEH)

X

17 Appendices

17.1. References

The Applicant's References: See Section 17.3

The FDA's References:
NA

17.2. 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 Study FOL-001 as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators.*

The FDA's Assessment:
The FDA agrees that the financial interests with clinical investigators have been disclosed.

Covered Clinical Study (Name and/or Number):* JCAR017-FOL-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 772		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5 (one of 5 disclosed both financial arrangements & proprietary interest)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 4		

Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in study: 0 Applicant of covered study: Celgene Corporation, a Bristol Myers Squibb Company		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

17.3. Applicant References

1 Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66(6):443-59.
2 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 22 Registries, Nov 2023 Sub (1975-2021).
3 Panayiotidis P, Follows GA, Mollica L, et al. Efficacy and safety of copanlisib in patients with relapsed or refractory marginal zone lymphoma. Blood Adv 2021;5:823-28.
4 Cerhan JR, Habermann TM. Epidemiology of marginal zone lymphoma. Ann Lymphoma 2021;5:1.
5 Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms [published correction appears in Leukemia 2023;37(9):1944 51. doi: 10.1038/s41375-023-01962-5]. Leukemia 2022;36(7):1720-48.
6 Rossi D, Bertoni F, Zucca E. Marginal-zone lymphomas. New Engl J Med 2022; 386:568-81.
7 Luminari S, Merli M, Rattotti S, et al. Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. Blood 2019;134(10):798-801.
8 Conconi A, Thieblemont C, Cascione L, et al. Early progression of disease predicts shorter survival in MALT lymphoma patients receiving systemic treatment. Haematologica 2020;105(11):2592-7.
9 Non-interventional Study Report for Study CA082-1206: A systematic literature review of clinical evidence of third line and later (3L+) treatments for marginal zone lymphoma in adult patients. Bristol-Myers Squibb Company; 2025. Document Control No. 930241335.
10 Cheah C, Seymour J. Marginal zone lymphoma: 2023 update on diagnosis and management. Am J Hematol. 2023;98:1645–1657.
11 Walewska R, Eyre TA, Barrington S, et al. Guideline for the diagnosis and management of marginal zone lymphomas: A British Society of Haematology Guideline. Br J Haematol 2024;204:86–107
12 Florindez JA, Chihara D, Reis IM, et al. Risk of transformation by frontline management in follicular and marginal zone lymphomas: a US population–based analysis. Blood advances 2024;8(16):44-32.
13 Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol 2019;37(14):1188-99.
14 Coleman M, Andorsky DJ, Yacoub A, et al. Patients with relapsed/refractory marginal zone lymphoma in the MAGNIFY Phase IIIb interim analysis of induction R2 followed by maintenance. Blood 2020;136(Supplement 1):24-25.
15 Opat S, Tedeschi A, Linton K, et al. The MAGNOLIA Trial: Zanubrutinib, a Next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res 2021;27(23):6323-32.
16 Lansigan F, Andorsky DJ, Coleman M, et al. Completed induction phase analysis of MAGNIFY: Phase 3b study of lenalidomide + rituximab (R2) followed by maintenance in relapsed/ refractory indolent non-Hodgkin lymphoma. Annual Meeting of the British Society for Haematology; April 3-5, 2022.
17 Lansigan F, Andorsky DJ, Coleman M, et al. P1156: MAGNIFY Phase 3b study of lenalidomide + rituximab (R2) followed by maintenance in relapsed/refractory indolent non-Hodgkin lymphoma: complete induction phase analysis. Hemasphere 2022;6(Suppl):1043-44.
18 Nastoupil LJ, Hess G, Pavlovsky MA, et al. Phase 3 SELENE study: ibrutinib plus BR/R-CHOP in previously treated patients with follicular or marginal zone lymphoma. Blood Adv 2023;7(22):7141-50.
19 Richardson NC, Kasamon Y, Pazdur R, et al. The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint. Lancet Oncol 2022;23(5):563-6.
20 Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory, indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022;23(1):91-103.
21 Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood 2024;143(6):496-506.

[22] Abramson JS, Palomba ML, Gordon LI, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood 2017;130(1): Abstract No. 581.
[23] Abramson J, Gordon L, Palomba M, et al. Updated safety and long-term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. J Clin Oncol 2018;36(15 suppl):7505.
[24] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-68.
[25] Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95.
[26] Beaumont H, Evans TL, Klifa C, et al. Discrepanices of assessments in a RECIST 1.1 phase II clinical trial - association between adjudication rate and variability in images and tumors selection. Cancer Imaging 2018;18(1):50.
[27] Möller J, Steyn T, Combrinck N, et al. Inter-observer variability influences the Lugano classification when restaging lymphoma. SA J Radiol 2018;22(1):1357.
[28] Opat S, Tedeschi A, Hu B, et al. Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study. Blood Advances 2023; 7(23): 6801-811
[29] Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.
[30] Primary Clinical Study Report for Study JCAR017-FOL-001 (Cohort 4 [R/R MZL]): A Phase 2, open-label, single-arm, multicohort, multicenter trial to evaluate the efficacy and safety of JCAR017 in adult subjects with relapsed or refractory indolent B-cell non-Hodgkin lymphoma (NHL). Bristol-Myers Squibb Company; 2025. Document Control No. 930241035.
[31] Ahuja K, Roy AM. Second primary malignancies in marginal zone lymphoma survivors. Blood 2024;144(Supplement 1):4402.
[32] Timilsina S, Damato A, Budhathoki N, et al. Characterization of second primary malignancies in mucosa-associated lymphoid tissue lymphomas: A SEER Database Interrogation. Clin Lymphoma Myeloma Leuk 2022;22(2):76-81.
[33] Yang Y, Yang Y, Yan S. Risk and survival of second primary malignancies following diagnosis of gastric mucosa-associated lymphoid tissue lymphomas: A population-based study. Curr Probl Cancer 2021;45(6):100735.
[34] Amiot A, Jooste V, Gagniere C, et al. Second primary malignancies in patients treated for gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma 2017;58(9):1-11.

FDA Grouped Terms For Adverse Events Analysis

Grouped Terms	Preferred Terms
Abdominal pain	Abdominal distension Abdominal pain Abdominal pain upper
Affective disorder	Anxiety Depressed mood Depression
Ataxia	coordination abnormal gait disturbance
Aphasia	Aphasia Dysarthria
Bacterial infection	Grouped per HLGT: Bacterial infectious disorders
Chest pain	Chest discomfort Chest pain Pleuritic pain
Delirium	Delirium Hallucination Irritability Disorientation Restlessness
Dizziness	Dizziness Presyncope
Edema	ascites, fluid retention hypervolaemia oedema peripheral peripheral swelling pleural effusion pulmonary oedema
Encephalopathy	confusional state dyscalculia, dysgeusia, dysgraphia, cognitive disorder Disturbance in attention, brain fog

	somnolence
Fatigue	Asthenia Fatigue
Fever	Pyrexia
Fungal infection	Grouped per HLGT: Fungal infectious disorders
Hemorrhage	Epistaxis Haematoma Cystitis haemorrhagic Upper gastrointestinal haemorrhage Contusion Subdural haematoma
Infections - pathogen unspecified	Grouped per high-level group term: Infections - pathogen unspecified
Inflammation	Inflammation Mucosal inflammation
Motor dysfunction	Fine motor function dysfunction Muscle spasms Muscle weakness Dysdiadokinesis
Musculoskeletal pain	Arthralgia Back pain Bone pain Flank pain Pain in extremity Neck pain Non-cardiac chest pain
Neuropathy peripheral	Peripheral sensory neuropathy Paraesthesia
Oral pain	Oral pain Oropharyngeal pain
Rash	Urticaria Rash maculopapular Rash pruritic
Renal failure	Acute kidney injury Blood creatinine increased Glomerular filtration rate decreased
Tachycardia	Sinus tachycardia Tachycardia

Thrombosis	Catheter site thrombosis Deep vein thrombosis Pulmonary embolism Subclavian artery thrombosis
Tremor	Tremor Intention tremor
Viral infection	Grouped per HLGT : Viral infectious disorders
Xerosis	Dry mouth, dry skin

17.4 JCAR-FOL-001 Cohort 4 study eligibility criteria

Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject has MZL histologically confirmed within 6 months of screening, as assessed by local pathology. Availability of adequate archival tumor biopsy tissue from the last relapse, with corresponding pathology report for retrospective central pathology confirmation of diagnosis is required. If archival sample is before the last relapse or there is no tissue or insufficient tissue available, a new tumor biopsy is required. Tissue from fine needle aspirate is not permitted.
2. Subject must have relapsed or refractory disease, as assessed by the investigator.
   a. Relapsed lymphoma is defined as relapse after an initial response of CR or PR to the prior therapy
   b. Refractory lymphoma is defined as a best response of SD or PD after prior therapy
3. Subject must have measurable disease as follows:
   a. For MZL subjects (Cohort 4) with PET non-avid disease should have at least one measurable nodal lesion greater than 2.0 cm in the long axis (PET-positive disease is not required for MZL) according to the 'Celgene interpretation of the Lugano Classification'. In cases where the subject has no measurable nodal lesions greater than 2.0 cm in the long axis at baseline, then the subject must have at least one measurable extranodal lesion.
4. Subjects must have received the following depending on cohort assignment
   a.Cohort 4 (3L+ MZL): received at least 2 prior systemic therapies, including at least

one line
of combination systemic therapy, therapy with an anti-CD20 antibody (eg, rituximab, obinutuzumab) and an alkylating agent, or relapsed after HSCT. Splenectomy for Splenic
MZL (SMZL) is considered as a line of therapy. Antibiotics for extranodal MZL (ENMZL) are
not considered as a prior line of therapy.
5. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
6. Subjects who have received previous CD19-targeted therapy must have CD19-positive
lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy
7. Subject has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Subject has adequate organ function, defined as:
a. Adequate bone marrow function to receive lymphodepleting chemotherapy, as assessed by the investigator
b. Serum creatinine ≤ 1.5 × age-adjusted upper limit of normal (ULN) OR calculated creatinine clearance (Cockcroft and Gault; refer to Appendix C) > 30 mL/min
c. Alanine aminotransferase (ALT) ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)
d. Adequate pulmonary function, defined as ≤ Grade 1 dyspnea according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 and oxygen saturation (SaO2) ≥ 92% on room air
e. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) performed within 4 weeks of determination of eligibility
9. Subject has adequate vascular access for leukapheresis procedure.
10. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
11. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
12. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage
in other individuals for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of
refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues and cells for transplantation.
13. Females of childbearing potential (FCBP1) subjects must:
a. Have 2 negative pregnancy tests as verified by the Investigator (one negative

serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 7 days prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence from heterosexual contact.

b. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective method from screening until at least 12 months after the lymphodepleting chemotherapy.

c. Agree to abstain from breastfeeding during study participation and for at least 12 months following lymphodepleting chemotherapy.

d. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy

14. Male subjects must:

a. Practice true abstinence (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for 12 months after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.

b. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Evidence of composite DLBCL and FL, or of transformed FL. Subjects with World Health Organization (WHO) sub-classification of duodenal-type FL

2. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study based on investigator's judgement.
3. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study based on investigator's judgement.
4. Any condition that confounds the ability to interpret data from the study based on investigator's judgement.
5. Central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study).
6. History of another primary malignancy that has not been in remission for at least 2 years,
with the exception of the following non-invasive malignancies:
- Basal cell carcinoma of the skin
- Squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Carcinoma in situ of the breast
- Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
- Other completely resected stage 1 solid tumor with low risk for recurrence
7. Previous treatment with alemtuzumab within 6 months of leukapheresis, or treatment

with fludarabine or cladribine within 3 months of leukapheresis.
8. Prior CAR T-cell or other genetically-modified T-cell therapy.
9. History of or active human immunodeficiency virus (HIV).
10. Active hepatitis B or active hepatitis C. Subjects with a negative PCR assay for viral load
for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or
anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy.
11. Uncontrolled systemic fungal, bacterial, viral or other infection (including tuberculosis)
despite appropriate antibiotics or other treatment.
12. Active autoimmune disease requiring immunosuppressive therapy.
13. Presence of acute or chronic graft-versus-host disease (GVHD).
14. History of any of the following cardiovascular conditions within the past 6 months prior
to signing the ICF: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease.
15. History or presence of clinically relevant central nervous system (CNS) pathology

not related to disease under study such as epilepsy, seizure, aphasia, stroke, cerebral edema,
severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
16. Subject is a pregnant or nursing (lactating) woman.
17. Subject has an intolerance to dimethyl sulfoxide (DMSO) and/or dextran
18. Progressive vascular tumor invasion, thrombosis, or embolism
19. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation
20. Subject has received or undergone the following:
a. Therapeutic doses of corticosteroids (defined as >20 mg/day prednisone or equivalent) within 7 days prior to unstimulated leukapheresis. Physiologic replacement, topical, and inhaled steroids are permitted.
b. Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) and intrathecal (IT) chemotherapy must be stopped ≥ 7 days prior to unstimulated leukapheresis.
c. Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide > 300 mg/m2, ifosfamide, bendamustine) 2 weeks prior to unstimulated leukapheresis.
d. Experimental agents within 4 weeks prior to signing the ICF unless no response or PD is documented on the experimental therapy and at least 3 half-lives have elapsed prior to unstimulated leukapheresis.
e. Ibrutinib, lenalidomide and PI3Ki within 3 half-lives prior to unstimulated leukapheresis
f. Immunosuppressive therapies within 4 weeks prior to leukapheresis and JCAR017 infusion (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor [TNF], anti-IL6, or anti-IL6R)
g. Donor lymphocyte infusion (DLI) within 6 weeks prior to JCAR017 infusion
h. Radiation within 6 weeks of leukapheresis. Subject must have progressive disease in irradiated lesions or have additional non-irradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated PET-positive lesions are present, is allowed up to 2 weeks prior to unstimulated leukapheresis.
i. Systemic immunostimulatory agents (including but not limited to interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to JCAR017 infusion.