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NDA/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-new indication
Application Number(s)	125714/227
Priority or Standard	Yes
Received Date(s)	11/30/23
PDUFA Goal Date	05/31/24
Division/Office	DCEH /OCE/MHB
Review Completion Date	5/15/2024
Established Name	Lisocabtagene maraleucel (JCAR017)
Trade Name	BREYANZI
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Code Name	JCAR017
Applicant	Juno Therapeutics, Inc. a Bristol-Myers Squibb Company
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+CART+cells and CD8+ CART+ cells in separate syringes.
Dosing Regimen	Single dose containing 90 to 110 × 10^6 CAR-positive viable T cells administered by intravenous infusion and preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy (LDC).
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) including a BTK inhibitor
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of therapy, including a BTK inhibitor

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Reviewers of Multi-Disciplinary Review and Evaluation (If Applicable)

Primary Clinical Reviewer (s)	Cassandra Moran, DO, MS Helkha Peredo-Pinto, MD, MPH
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Bioresearch Monitoring (BIMO) reviewer	Yakubu Wangabi
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MORE= Medical Oncology Review
MHB=Malignant Hematology Branch
DCEH=Division of Clinical Evaluation Hematology
OCE: Office of Clinical Evaluation

Glossary

Term	Definition
2L+	second-line therapy or later
3L+	third-line therapy or later
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
ATA	antitherapeutic antibody
AUC	area under the concentration vs time curve
B-NHL	B-Cell Non-Hodgkin Lymphoma
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BMB	bone marrow biopsy
BMS	Bristol-Myers Squibb
BOR	best overall response
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR	chimeric antigen receptor
CBER	Center for Biologics Evaluation and Research
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CD19	cluster of differentiation 19
CD20	cluster of differentiation 20
CD28	cluster of differentiation 28
CFR	US Code of Federal Regulations
chemo	chemotherapy
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	maximum (or peak) concentration
CNS	central nervous system
COA	clinical outcomes assessment
COVID-19	coronavirus disease 2019
CR	complete response
CrCL	creatinine clearance
CRF	case report form
CRMTS	CBER Regulatory Meeting Tracking System
CRP	C-reactive protein
CRR	complete response rate
CRS	cytokine release syndrome
CRu	unconfirmed complete response
CT	computed tomography
CTCAE	Common Terminology Criteria Adverse Events
DBL	database lock
DL1S	dose level 1: 50 × 10^6 CAR+ T cells single-dose regimen
DL2S	dose level 2: 100 × 10^6 CAR+ T cells single-dose regimen
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	data safety monitoring board
EAS	Efficacy Analysis Set
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	electronic case report form
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire- Core measure 30 Items
EOS	end of study
EQ-5D-5L	EQ-5D health state classifier to 5 Levels
ETASU	Elements to Assure Safe Use
EuroQol	European Quality of Life
FDA	Food and Drug Administration

Term	Definition
FDG	fludeoxyglucose-18
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
FL3B	follicular lymphoma grade 3B
GBDS	Global Biometric and Data Sciences
GCP	Good Clinical Practices
GM-CSF	granocyte-macrophage colony-stimulating factor
HEOR	Health Economics & Outcomes Research
HGL	High grade B-cell lymphoma
HLA	human leukocyte antigen
HLGT	High level group term
HLH	Hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	Heath-related quality of life
HRU	hospital resource utilization
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICU	intensive care unit
IFN-γ	interferon gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
iiNT	investigator-identified neurologic toxicity
IL	Interleukin
IRC	Independent Review Committee
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	Intravenous
IWRC	International Workshop Response Criteria
KM	Kaplan-Meier
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LLOD	lower limit of detection
LOD	limit of detection
LoT	line(s) of therapy
LSLV	last subject last visit
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
Max	maximum
MCL	mantle cell lymphoma
mCRM	modified continual reassessment method
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activites
mPFS	median progression-free survival
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NE	not evaluable
NESI	neurotoxicity event of special interest
NHL	Non-Hodgkin's lymphoma
NOS	not otherwise specified
NR	not reported
NT	neurotoxicity
ORR	overall response rate
OS	overall survival
PAS	Primary Analysis Set
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK/PD	pharmacokinetics/pharmacodynamics
PMBCL	primary mediastinal B-cell lymphoma
PMR	postmarketing requirement
PO	orally
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PS	performance status/score

Term	Definition
PT	preferred terms
Q1, Q3	interquartile range
QoL	quality of life
qPCR	quantitative real-time polymerase chain reaction
R-CHOP	Chemotherapy regimen: cyclophosphamide, hydroxydaunorubicin, oncovir, prednisone
R/R	relapsed/refractory
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategies
RR	response rate
RWD	real-world data
SAA	serum amyloid A
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome-associated coronavirus 2
SAS	Statistical Analysis Software
sBLA	Supplemental Biologics License Application
SC	Steering Committee
SCS	Summary of Clinical Safety
SD	stable disease
SLL	small Lymphocytic Lymphoma
SLR	systematic literature review
SMQ	standardized MedDRA query
SOC	system organ class
SPD	sum of the products of diameters
SPM	second primary malignancy
SRC	Safety Review Committee
StD	standard deviation
TEAE	treatment-emergent adverse event
TE-SAE	treatment-emergent serious adverse event
THRBCL	T-cell/histiocyte-rich large B-cell lymphoma
TLS	tumor lysis syndrome
TNE	transplant ineligible
Tmax	time at which maximum concentration (Cmax) occurs
US	United States
U/L	units per liter
USPI	United States Prescribing Information
VAS	visual analog scale

1 Executive Summary

1.1. Product Introduction

On November 30, 2023, Juno Therapeutics (the Applicant) submitted a supplemental Biologic License Application (sBLA), seeking a new indication for BREYANZI (lisocabtagene maraleucel, hereafter referred to as liso-cel) for treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after a Bruton's tyrosine kinase inhibitor (BTKi).

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 chimeric antigen receptor (CAR) that consists of anti-CD19 single-chain variable fragment, a CD28 effector domain, and a 4-1BB co-stimulatory domain. The FDA review team recommends traditional approval of liso-cel for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. The recommended one-time dosage of liso-cel is 90 to 110 x 10^6 CAR-positive viable T cells, administered by intravenous infusion. Liso-cel is currently approved for treatment of adult patients with:

1) Relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma (FL) grade 3B (traditional approval on February 5, 2021).
2) LBCL, including DLBCL NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B (traditional approval on June 24, 2022):
    a) Disease refractory to first-line chemoimmunotherapy or who relapse within 12 months of first line chemoimmunotherapy; or
    b) Disease refractory to first-line chemoimmunotherapy or who relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
3) R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a BTKi and a B-cell lymphoma 2 inhibitor (accelerated approval on March 14, 2024).
4) Adult patients with FL after two or more prior lines of systemic therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was demonstrated in Study 017001 MCL Cohort

(TRANSCEND MCL), an open-label, multicenter, single-arm trial of liso-cel in adult patients with R/R MCL who had received at least 2 prior lines of therapy, including a BTKi, an alkylating agent, and an anti-CD20 agent. The study included patients with Eastern Cooperative Oncology Group (ECOG) performance status/score (PS) of ≤1, prior autologous and/or allogeneic HSCT, and CNS lymphoma involvement. The study excluded patients with a creatinine clearance ≤30 mL/min, alanine aminotransferase >5 times the upper limit of normal, or left ventricular ejection fraction (LVEF) <40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. The planned dose of liso-cel was 100×10^6 CAR-positive viable T cells. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. Liso-cel was administered 2 to 7 days following completion of lymphodepleting chemotherapy. The lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day concurrently for 3 days.

Efficacy:

Efficacy was established in subjects who received at least 2 prior lines of systemic therapy including a BTKi based on overall response rate (ORR) with durability as determined by an independent review committee (IRC) per Lugano 2014 criteria (Cheson et al. 2014). In the efficacy analysis population (N=68), the ORR was 85.3% (95% confidence interval [CI]: 74.6, 92.7) with a median time to response of 1 month (range: 0.7 to 3 months). The complete response (CR) rate was 67.6% (95% CI: 55.2, 78.5) and a partial response (PR) rate was 17.6% (95% CI: 9.5, 28.8). The estimated median duration of response (DOR) was 13.3 months (95% CI: 6.0, 23.3). Among 46 patients achieving CR, the estimated rate of continued response at 12 months was 57.8% (95% CI: 41.9, 70.7) and 18 months 48.0% (95% CI: 31.6, 62.6). In the 89 leukapheresed patients, ORR was 73.0% (95% CI: 62.6, 81.9) with a CR rate of 57.3% (95% CI: 46.4, 67.7) and a PR rate of 15.7% (95% CI: 8.9, 25.0).

In this heavily pre-treated population with limited available effective therapies, the high ORR and complete response rate (CRR) supported by durability of response supports the determination that liso-cel provides a clinically meaningful benefit in patients with R/R MCL who have received at least 2 prior lines of therapy including a BTKi supporting traditional approval.

Safety:

The Study 017001 MCL Cohort was the primary source for safety data and included a total of 88 subjects with R/R MCL who had received at least two prior systemic therapies including a BTKi, and were treated with liso-cel. Cytokine release syndrome (CRS) and neurotoxicity (NT) are the most common toxicities of liso-cel. The product carries a boxed warning for these toxicities. There is a risk evaluation and mitigation strategy (REMS) that includes Elements to Assure Safe Use (ETASU). The safety profile was similar, including for events of CRS and NT, in patients with R/R MCL as

compared to a larger integrated safety population composed of patients with R/R LBCL, CLL/SLL, FL, MCL, and Marginal Zone lymphoma (MZL); no new safety signals were identified. Of the 88 subjects who received liso-cel after at least 2 prior lines of therapy for R/R MCL including a BTKi, CRS occurred in 61% (54/88), including Grade 3 in 0% and Grade 4 in 1.1% of subjects. CAR T cell-associated NT occurred in 31% (27/88), including 7.9% (7/88) Grade 3 and 1% (1/88) Grade 4. One subject had ongoing NT at time of death due to another cause, and one subject had ongoing Grade 4 CRS at time of death that was thought to be due to tumor lysis syndrome. Treatment-emergent serious adverse events (SAEs) occurred in 53% of patients. While severe CRS and NT associated with liso-cel can be life-threatening, treatment algorithms to mitigate these AEs, as implemented in the study, allow the benefits of treatment to outweigh the risks.

Conclusion

Study 017001 MCL Cohort represents an adequate and well-controlled trial. The magnitude of benefit based on high response rate and duration of response, along with high complete response rate in the proposed population, forms the basis for substantial evidence of effectiveness in the context of an acceptable safety profile. Further, the confirmatory evidence of activity of liso-cel in MCL is supported by both a clear mechanistic rationale and the fact that liso-cel has been approved for treatment of other CD19 expressing hematologic malignancies based on other adequate and well-controlled studies. Given the life-threatening nature of R/R MCL and lack of standard of care, the high response rate of 85.3% and durability of responses, with a median duration of response of 13.3 months, observed with liso-cel represents a clinical benefit in the intended patient population. The adverse events of CRS and NT, if managed appropriately, represents toxicities that are acceptable from a benefit-risk perspective. Thus, the overall benefit-risk profile of liso-cel supports a traditional approval in adult patients with R/R MCL after at least 2 prior lines of systemic therapy, including a BTKi.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The benefit-risk assessment for lisocabtagene maraleucel (liso-cel) for the indicated population is based on the results of Study 017001 MCL Cohort, an open-label, multicenter, single-arm trial of liso-cel in adult patients with relapsed or refractory mantle cell lymphoma (R/R MCL) who had received at least 2 prior lines of therapy including a Bruton's tyrosine kinase inhibitor (BTKi), an alkylating agent, and an anti-CD20 agent. A total of 68 patients with R/R MCL constituted the efficacy analysis population. The primary efficacy endpoint is overall response rate (ORR) determined by independent response committee as per 2014 Lugano Criteria (Cheson et al. 2014). Key secondary efficacy outcome measures included duration of response (DOR) and complete response rate.

The totality of the data from Study 017001 MCL Cohort demonstrates a favorable benefit-risk profile for liso-cel as a treatment for patients with R/R MCL who have received at least 2 prior lines of therapy, including a BTKi.

Efficacy: Study 017001 MCL Cohort demonstrated clinically meaningful efficacy of liso-cel based on ORR of 85.3 (95% CI: 74.6, 92.7) and supported by durability of response (median DOR: 13.3 months, 95% CI: 6.0, 23.3) in a patient population with limited treatment options.

Safety: The risks of liso-cel are associated with its mechanism of action and with the toxicities of the lymphodepletion regimen. Cytokine release syndrome and neurotoxicity can be life-threatening or fatal. Hypogammaglobulinemia can persist for months and requires monitoring and potential intervention. However, these risks can be managed adequately with appropriate risk mitigation strategies. Safety results from Study 017001 MCL Cohort demonstrate an acceptable toxicity profile for liso-cel.

Overall benefit-risk assessment:
Liso-cel has an overall favorable benefit-risk profile in patients with R/R MCL who have received at least 2 prior lines of therapy, including a BTKi. Based on ORR supported by durability of responses, liso-cel has demonstrated meaningful clinical benefit, and hence supports a traditional approval for intended population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Mantle cell lymphoma (MCL) is an aggressive B cell malignancy. • MCL makes up 6% of non-Hodgkin lymphomas; incidence is 1-2 per 100,000, 3:1 Male:Female. • Initial response rates to treatment are high, but relapse is common. • Outcomes for patients with relapsed or refractory (R/R) disease are poor. Patients who progress after BTKi have a particularly poor outcome with median OS of 6-10 months (Kumar et al. 2019).	R/R MCL is a serious condition with a poor prognosis and tendency to relapse.
Current Treatment Options	• There is no clearly established standard of care for treatment of R/R MCL. • Some patients cannot tolerate available salvage therapies due to age or comorbidities. • The most recently approved R/R MCL therapies are Bruton's tyrosine kinase (BTK) inhibitors and chimeric antigen receptor (CAR) T cell therapy, which are in confirmatory studies under accelerated approval. BTK inhibitors require daily therapy until treatment failure (Wang et al. 2023). Limitations include severe toxicities including arrythmias, infections, bleeding, and hypertension. Limitations with CAR T cell therapy include severe and potentially fatal toxicities as well as logistical constraints with delays in therapy which may be especially problematic for patients with rapidly progressive disease.	Safe, effective salvage treatments are needed for R/R MCL.
Benefit	• 017001 Cohort MCL is a single arm, multicenter study of liso-cel for the treatment of adults with R/R MCL who had previously received 2 prior lines of therapy including a BTK inhibitor.	Study 017001 demonstrated a clinically significant ORR with durable responses in this difficult-to-treat patient population, supporting the determination that liso-cel

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Lymphodepleting chemotherapy was followed by a single infusion of liso-cel. • The primary endpoint of overall response rate (ORR) per independent review committee (IRC) was evaluated in 68 subjects with at least 6 months of follow-up after their first objective disease response. • Key efficacy results were: – ORR 85.3% (95% CI: 74.6, 92.7) – Complete response (CR) rate 67.6% (95% CI: 55.2, 78.5) – Median time to response 1 month (range: 0.7 to 3 months) • Median duration of response (DOR) was 13.3 months (95% CI: 6.0 23.3).	has clinically meaningful activity in patients with R/R MCL who have received at least 2 prior lines of therapy, including a BTK inhibitor.
Risk and Risk Management	• Major adverse events associated with liso-cel were cytokine release syndrome (CRS), neurologic toxicities, prolonged cytopenias, infectious complications, and hypogammaglobulinemia. • The most substantial risks of liso-cel are CRS and neurologic toxicity, which were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks of secondary malignancy associated with this genetically modified immunotherapy based on the potential for replication competent retrovirus and insertional mutagenesis.	All the evidence indicates that the risk of liso-cel, while substantial, does not outweigh the benefit to adult patients with R/R MCL. Furthermore, there is currently in place a risk evaluation and mitigation strategy (REMS) that includes Elements to Assure Safe Use (ETASU).

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	Section 8.1.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

It was estimated that approximately 80,500 new cases of NHL were to be diagnosed and approximately 20,180 patients were to die of the disease in the US in 2023.[1] MCL is an aggressive form of NHL that comprises between 6% and 8% of all NHL cases.[2] The disease occurs more commonly among elderly men, with a median age at diagnosis of 67 years, and a male to female ratio of 7:3.[3] MCL is characterized by the t(11;14) chromosomal translocation that results in Cyclin D1 overexpression in pre-B cells. Cytologic subtypes of MCL include classic MCL, pleormorphic subtype, and the blastoid subtype, with the variants usually having a more aggressive natural history.[4] Patients who have high risk features such as TP53 mutation, blastoid histology, high tumor proliferation index, complex karyoptype, refractory disease and secondary CNS involvement tend to have poorer outcomes compared to patients who do not have any of these high-risk features. MCL is considered incurable with standard immunochemotherapy and is associated with a multiply relapsing disease course and poor long-term survival.[5, 6] Across reported results from clinical trials, median duration of remission from initial diagnosis is approximately 5 years, with median OS ranging from 3 to 10 years[7] and progressively worsening after each line of therapy.[8]

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the condition. However, the prognostic significance of the noted high-risk features for patients with R/R MCL, as enrolled in this trial, are less well-understood as compared to the frontline setting.

MCL is a rare and aggressive form of non-Hodgkin lymphoma (NHL) comprising approximately six percent of all NHL in the United States, generally considered incurable. MCL occurs more frequently in older adults, with a median age at diagnosis of 60 to 70 years of age with males affected more often than females (3 to 1) (Lynch et al. 2024), and White patients are diagnosed more often than other races. A large national cancer database report consisting of over 34,000 patients diagnosed with MCL between 2004 and 2020 noted that 93% patients were White and 4.2% were Black (Vardell et al. 2023). Black patients had MCL diagnosed at younger age and had lower overall survival following MCL diagnosis. One retrospective study based on the Texas Cancer Registry database (296 Hispanic, 1556 non-Hispanic subjects) from 2006-2016 described the following demographics for non-Hispanic subjects: 92.5% White, 5.3% Black, 1.5% Asian, 0.4% Native American and 0.1% with unknown race; additionally, 72.6% of Hispanic and 72.7% of non-Hispanic subjects were male (Song et al. 2020a).

Frontline therapy is usually determined based on age, PS, and suitability for autologous stem cell transplantation (ASCT), and treatment includes chemoimmunotherapy consisting of cytotoxic agents along with anti-CD20 monoclonal antibody. However, the prognosis is generally poor, particularly for relapsed or refractory MCL, where effective options are limited and standards of care are lacking.

2.2. Analysis of Current Treatment Options

Standard Treatments for Relapsed or Refractory MCL

Frontline treatment options for patients with newly diagnosed MCL are usually defined by age, performance status, and suitability for ASCT.9 Frontline (1L) treatment almost always includes a regimen of cytotoxic agents along with anti-CD20 monoclonal antibody. Because MCL is an aggressive lymphoma, optimal frontline treatment for symptomatic, young (< 65 years old) and fit patients, involves more intensive immunochemotherapy regimens, including HDCT and ASCT, with the goal of obtaining longer remissions. For these patients per NCCN guidelines v5.20239, 1L therapy can also include the use of BTKi (during induction therapy and during maintenance after ASCT or aggressive induction therapy in association with rituximab) on the basis of the recent Phase 3 RCT TRIANGLE results.[10]

Due to the later onset of the disease, most patients are elderly at the time of diagnosis and are not suitable for transplant. For these patients the preferred regimens include BR (bendamustine, rituximab), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone), lenalidomide and rituximab, RBAC500 (rituximab, bendamustine, cytarabine). Maintenance therapy with rituximab may be suitable as well for these patients who received less aggressive 1L therapy without any consolidation therapy.9

For patients with MCL, no curative options exist, and most patients require multiple lines of salvage therapy in their lifetime. Outcomes after each line of therapy progressively worsen: median PFS and median OS, respectively, are 4.0 years and 9.7 years after 1L therapy; 14.0 months and 41.1 months after 2L therapy; 6.5 months and 25.2 months after 3L therapy; and 5.0 months and 14.4 months after 4L therapy.[8]

There is no single standard-of-care treatment for R/R MCL, the optimal approach/sequence to treat R/R MCL is yet to be defined, and there is a lack of data comparing the available treatment options in a randomized controlled fashion. Bortezomib and lenalidomide are the only 2 agents with FDA regular approval for the treatment of R/R MCL. In particular, bortezomib was initially approved for R/R MCL after 1 prior LoT and has been recently approved also for 1L treatment of adult patients with MCL. Lenalidomide is approved for patients with MCL whose disease has relapsed or progressed after 2 prior therapies (including bortezomib). In the R/R setting, the 2 agents showed ORR ranging between 26% and 31% with CR + Cru rate between 7% and 8%, and median DOR from 9.3 months to 16.6 months (Table 1).

In recent years, 3 covalent BTKi therapies (ibrutinib,[11] acalabrutinib,[12] and zanubrutinib[13]) have received FDA accelerated approval for R/R MCL. Although results with these agents are encouraging (Table 1), definitive results from the confirmatory trials are awaited. Subsequently, on 06-Apr-2023, the FDA accelerated approval of ibrutinib for the treatment of patients with R/R MCL who have received at least 1 prior therapy was voluntarily withdrawn by the sponsor[14] based on a lack of OS advantage associated with ibrutinib therapy and on the increased adverse reactions in combination with chemoimmunotherapy among patients with previously untreated MCL in the Phase 3 SHINE RCT.[15] Acalabrutinib and zanubrutinib continue to be recommended 2L therapies for R/R MCL per NCCN guidelines9 based on their robust efficacy data (ORR between 80% and 84%, CRR between 40% and 59%, and median DOR between 19.5 months and not reached).

Nonetheless, development of resistance or intolerance to covalent BTKi therapies is common, typically occurring within 18 months to 24 months.[16] In addition, BTKi therapies require continuous administration, and toxicities from long-term use of BTKis may not be tolerable for all patients, thus limiting their long-term administration. Even selective BTKis such as acalabrutinib have cardiac toxicities, with more than an 8-fold increase in ventricular arrythmias and sudden cardiac death with acalabrutinib compared with non-BTKi therapies, which preclude prolonged use for the treatment of R/R MCL.[17]

In the R/R setting, per NCCN guidelines, 2L+ treatment regimens include preferred regimens (covalent BTKis alone [acalabrutinib or zanubrutinib] or lenalidomide in combination with rituximab) and other recommended regimens (ibrutinib ± rituximab).9 Other regimens (useful in certain circumstances such as lack of prior exposure) include bortezomib ± rituximab, venetoclax ± rituximab, ibrutinib + venetoclax and different combination of chemoimmunotherapies (including rituximab).

Pirtobrutinib (JAYPIRCA®), a noncovalent BTKi, has been recently granted FDA accelerated approval in Jan-2023 for the treatment of adults with R/R MCL after ≥ 2 lines of systemic therapy, including a BTKi, based on the single-arm BRUIN study which showed ORR of 50%, CRR of 13%, and median DOR of 8.3 months in patients with R/R MCL post-BTKi treatment (Table 1).[18],[19],[20] In addition to the limited efficacy, pirtobrutinib also carries the burden of a continuous daily administration and of significant toxicity, including Grade 3-4 events of cardiac toxicity (1.0% with atrial fibrillation or flutter), hemorrhage (2.4%), infections (17%), and cytopenias including neutropenia (24%), anemia (11%), and thrombocytopenia (11%). Adverse reactions led to dosage reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation in 9% of subjects.

Brexucabtagene autoleucel (KTE-X19; TECARTUS®; hereby referred as brexu-cel), an autologous CD19-directed CAR T-cell therapy, received FDA accelerated approval in 2020 for treatment of R/R MCL based on the single-arm ZUMA-2 study.[21] This pivotal Phase 2 study eligibility criteria included subjects with R/R MCL with a maximum of 5

prior regimens and no prior allogenic HSCT, no major comorbidities (only subjects with mild impaired kidney function or LVEF ≥ 50% were eligible), no secondary CNS involvement and predefined minimum threshold for hematological values. At a median follow-up of 35.6 months, treatment with brexu-cel resulted in favorable outcomes: 91% ORR, 68% CRR, 28.2 month median DOR, 25.8 month median PFS, and 46.6 month median OS.[22] Recent RWD showed ORR and CR rates of 90% and 82%, respectively, in 168 US patients who received brexu-cel and a median of 3 prior LoT (range 1-10), of whom 86% were BTKi-exposed. At a median follow-up of 14.3 months after infusion, the median DOR was 17.2 months, median PFS was 16.4 months, and median OS was NR. No difference in response rates, PFS, or OS were observed between BTKi-include and BTKi-exposed patients. However, RWD show a < 6 month median PFS for brexu-cel-treated patients with high-risk simplified mantle cell international prognostic index or *TP53* mutation.[23] Furthermore, based on the ZUMA-2 study, brexu-cel is associated with high rates of Grade ≥3 AEs, including prolonged cytopenias (55%), infections (30%), neurologic toxicities (37%), and CRS (18%) which limit its use in a primarily elderly population with comorbidities.21

Table 1: Applicant – Summary of FDA-approved Treatments for MCL

Drug Name (Generic)	Initial Appro-val	Indication	ORR, % (95% CI)	CRR, % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	OS, months (95% CI)
Standard Approval							
Velcade® (bortezomib)	2003	Adult patients with:					
		Previously untreated MCL, Velcade combined with R-CAP vs R-CHOP (randomized study)	88 (83, 92) vs 85 (80, 89)[a]	44 (38, 51) vs 34 (28, 40)	--	25 (20, 32) vs 14 (12, 17) (HR: 0.63; 0.50, 0.79)	91 (71, NE) vs 56 (47, 69) (HR: 0.66; 0.51, 0.85)
		R/R MCL after 1 prior line of therapy (single arm study)	31 (24, 39)[a]	8 (4, 13)[b]	9.3 (5.4, 13.8)[c]	--	--
Revlimid® (lenalidomide)	2005	Adult patients with MCL relapsed or refractory to bortezomib or a bortezomib-containing regimen (single arm study)	26 (18.4, 33.9)[a]	7 (3.1, 12.5)[b]	16.6 (7.7, 26.7)[c]	--	--
Accelerated Approval							
Imbruvica® (ibrutinib) *Approval withdrawn in May 2023*	2013	Adults with MCL who have received at least 1 prior therapy (single-arm study)	65.8 (56.2, 74.5)	17.1	17.5 (15.8, NE)	--	--
Calquence™ (acalabrutinib)	2017	Adult patients with MCL who have received at least 1 prior therapy (single arm study)	80 (72, 87)	40 (31, 49)	NE	--	--
Brukinsa® (zanubrutinib)	2019	Adult patients with MCL who have received at least 1 prior therapy (single arm study)	84 (74, 91)	59 (-)	19.5 (16.6, NE)	--	--
Tecartus® (brexu-cabtagene autoleucel)	2020	Adult patients with relapsed or refractory MCL (single arm study)	87 (75, 94)	62 (48, 74)	NR (8.6, NE)	--	--
Jaypirca® (pirtobrutinib)	2023	Adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTKi (single arm study)	50 (41, 59)	13	8.3 (5.7, NE)	--	--

[a] ORR (IWRC) : CR +Cru +PR ; [b] CRR (IWRC) : CR+Cru ; [c] DOR : CR + Cru + PR
Note: Tumor response assessed according to IWRC 1999 (Velcade, Revlimid) or the 2014 Lugano Classification (Calquence, Brukinsa, Tecartus, and Jazpirca).

Unmet Medical Need

MCL is an aggressive form of NHL that is considered incurable with standard chemotherapy and is associated with a multiply-relapsing disease course and poor long-term survival. No curative options exist for MCL patients, and outcomes after each line of therapy progressively worsen; for example, median PFS and OS, respectively, decrease from 14.0 and 41.1 months after 2L therapy to 5.0 and 14.4 months after 4L therapy.8

Outcomes in patients with disease progression after ≥ 2L therapy, and in particular following covalent BTKi treatment, are poor. Resistance and intolerance (due to known toxicities[24]) to BTKi treatments are common and limit the ability to treat patients with a second covalent BTKi. The majority of R/R MCL patients post-BTKi treatment die of their disease. Although data in the post-BTKi R/R MCL population are limited, recent retrospective analyses of immunochemotherapy use after ibrutinib showed ORR of 20% to 42%, CRR of 7% to 22%, median DOR of 3 months to 5.8 months, median PFS of 1.9 months to 3.2 months, and median OS of 2.5 months[25] to 11 months[26]. Collectively, retrospective and RWD demonstrate that patients with BTKi-pretreated MCL continue to be a population of high unmet need, irrespective of how heavily pretreated their disease may be. Not only do less than half go on to receive subsequent therapy, but when they do, effective treatment options for these patients post-BTKi treatment are particularly limited:

- From a RWD assessment of treatment outcomes of 303 US MCL patients who received prior BTKi, 142 (46.9%) of these patients received subsequent therapy after BTKi treatment, with a median time to discontinuation of subsequent therapy or death of 3.8 months. Median OS for all patients post-BTKi treatment was 8.2 months.[27]
- In a retrospective data collection from a US oncology database among 739 MCL patients who discontinued BTKi treatment for MCL, 352 (47.6%) patients received at least 1 post-BTKi treatment, and median duration of the immediate post-BTKi treatment was 2.6 months. Among the 739 patients who discontinued covalent BTKi treatment, the median time from covalent BTKi discontinuation to next treatment discontinuation or death was 3.9 months, and the median overall survival was 10.3 months.[28]
- In a retrospective chart review study of 240 EU patients who received prior BTKi, 149 (62%) received subsequent therapy after BTKi, with a median OS from initiation of first post-BTKi treatment of 9.7 months (95% CI: 6.3, 12.7; 27.3 months median follow-up).[29]
- In a retrospective cohort study of 211 patients who received ibrutinib as 2L therapy within UK's National Health Service, 100 patients experienced PD (152 in total discontinued BTKi). Among the 43% of patients who received further systemic therapy, median post-BTKi OS was 11.6 months (95% CI: 6.8, 16.5) vs 0.4 months (95% CI: 0.2, 0.5, p ≤ 0.001) among those who received no

subsequent therapy. In the total population, the median OS from BTKi discontinuation was 1.4 months (95% CI: 0.6, 2.2).[30]

- In a retrospective cohort study from a Japanese administrative database of 247 patients who received BTKi therapy, 137 (55.5%) received subsequent therapy. The median OS from the end of ibrutinib therapy in patients regardless of the receipt of post-ibrutinib therapy (N = 247), in those who did not receive post-ibrutinib therapy (n = 110), and in those who received post-ibrutinib therapy (n = 137) was 5.6 months (95% CI: 3.8, 8.7), 2.3 months (95% CI: 1.2, 3.9), and 8.7 months (95% CI: 5.6, 13.8), respectively.[31]

An SLR[32] was conducted for the period up to 19-Sep-2022 on NCCN recommended treatments for 3L+ MCL patients previously treated with BTKi; specifically, patients with non-specific regimens, non-specific prior number of lines of therapy, and non-NCCN-recommended regimens were excluded. A total of 9 unique studies were identified for inclusion, including 5 studies investigating immunochemotherapies (1 clinical trial and 4 observational studies) and 4 studies investigating brexu-cel. Among the non-CAR T studies, a clinical trial with a subgroup of 15 patients in 3L+ MCL post-BTKi showed an ORR of 53% with bendamustine + rituximab. Two of the other 4 observational retrospective non-CAR T studies reported ORRs of 27% and 83%, and 1 study reported a median DOR of 4.6 months. Small sample size, heterogeneous population and other limitations in study design may contribute to mixed results. Overall, the results suggest a lack of standard of care in the 3L+ setting for MCL.

Therapeutic options for R/R MCL are being further limited by the earlier use of BTKi in the frontline setting. Indeed, NCCN guidelines and recent RWD reports support the effectiveness of the use of BTKi in combination with chemotherapy and anti-CD20 antibody in the 1L setting during induction therapy for patients who are candidates for HDCT/ASCT and during maintenance after HDCT/ASCT or after aggressive therapy. In addition, use of BTKi therapies in the 1L setting is further being explored in multiple ongoing clinical trials.9,[3334] The earlier use of BTKi therapies may limit the non-CAR T therapeutic options for subjects with R/R MCL to the agents with full regular FDA approval (lenalidomide and bortezomib), which have shown limited efficacy and are often associated with significant toxicities. The other NCCN-recommended regimens are not preferred in 2L and may be useful only in certain circumstances.9 Pirtobrutinib, on the other hand, only has accelerated approval, has shown limited benefit, and is not approved for use in the 2L setting.

The Applicant's Position:

CAR T-cell therapies in general offer greater benefit to R/R MCL patients with the potential of long-term remission and cure, as well as the advantage of single dosing. While response and the depth of response to brexu-cel CAR T-cell treatment are greater versus conventional therapies in the R/R MCL setting, the rates of brexu-cel's associated toxicities (Grade ≥ 3 cytopenias, infections, neurologic toxicity, and CRS) may limit its wider suitability in the R/R MCL patient population that presents with

advanced median age and comorbidities.

Therefore, there remains a critical unmet need for a CAR T-cell therapy alternative with robust and durable responses and an improved tolerability profile versus currently approved options for R/R MCL patients after BTKi treatment. Liso-cel could meet the emerging need for treatment options in R/R MCL after a BTKi.

The FDA's Assessment:

The FDA agrees with the Applicant's description of current treatment options and that patients with R/R MCL previously treated with a BTKi have limited effective treatment options. Ibrutinib was the first BTKi to achieve accelerated approval for patients with R/R MCL, however the indication was voluntarily removed after a phase III trial evaluating ibrutinib in combination with chemotherapy in patients with previously untreated MCL failed to confirm clinical benefit. Recently several next-generation BTKi agents (zanubrutinib, acalabrutinib and pirtobrutinib) and an anti-CD19 CAR T cell product (brexucabtagene autoleucel) received accelerated approval for use in the second and greater line MCL setting. Confirmatory trials are ongoing, and BTKi therapy is an accepted and recommend SOC for patients with MCL. However, there are limitations to BTKi therapy, which require continuous treatment until progression and are associated with low complete response rates. Limitations include resistance to therapy and significant toxicities such as cardiac arrythmias, bleeding, and infection which are well described for BTKi therapy particularly with longer term use, which may result in treatment discontinuation due to unacceptable toxicity. While the addition of BTKis to the MCL treatment armamentarium is significant, an unmet medical need remains for patients who have failed standard of care immunotherapy and standard of care salvage therapies such as BTKis.

Available treatment options after BTKi therapy failures are especially limited and patient survival is measured in months (Wang et al. 2013; Wang et al. 2018; Song et al. 2020b). Current therapies for patients who have received a prior BTKi, may include another BTKi or other therapies that may be associated with significant toxicities.

Regarding the Applicant's statement that CAR T therapies in general offer greater benefit to patients with R/R MCL due to a one time therapy approach; the FDA notes that in addition to the important challenges with anti-CD19 CAR T cell therapy, including logistical constraints leading to delays in therapy, limitations to access therapy, severe toxicities, and limited long-term efficacy data, the benefit of CAR T therapy compared to SOC options such as chemoimmunotherapy and BTKi therapy in the earlier line setting has not been established. The FDA agrees, in general, with the Applicant's statement that there may be advantages to a single use therapy such as CAR-T in patients with heavily pretreated MCL. Currently, the only approved CAR T therapy for R/R MCL is brexucabtagene autoleucel (Tecartus) which received accelerated approval for the treatment of adult patients with R/R MCL who have received at least 2 prior lines of therapy where a confirmatory trial(s) is needed to confirm benefit in this broad

population (i.e., (b) (4)) and to demonstrate durability.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

BREYANZI® (liso-cel) is currently approved in the US for the treatment of adult patients with LBCL, including DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy *(sBLA 125714/90; 24-Jun-2022 approval)*; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age *(sBLA 125714/90; 24-Jun-2022 approval)*; or
- relapsed or refractory disease after two or more lines of systemic therapy *(BLA 125714/0; 04-Feb-2021 approval)*.

The FDA's Assessment:

Liso-cel is currently approved for treatment of adult patients with:

- large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
  - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy (traditional approval on June 24, 2022); or
  - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age (traditional approval on June 24, 2022); or
  - relapsed or refractory disease after two or more lines of systemic therapy (traditional approval on February 5, 2021).

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

- relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a

Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor (accelerated approval on March 14, 2024).

- relapsed or refractory follicular lymphoma (FL) who have received at least 2 prior lines of therapy (accelerated approval on May 15, 2024).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2: Applicant – Regulatory History of BREYANZI in R/R MCL

Date	Activity and Purpose	Key FDA Feedback
29-May-2015	Initial IND 016506 submitted with Protocol 017001, a multi-cohort study including MCL Cohort	IND 016506 Study may proceed received (26-Jun-2015)
20-Apr-2021)	Type B Format and Content Meeting (CRMTS #13176 To gain the Agency's feedback on the following: the planned sample size and follow-up needed for registration in R/R MCL, the primary endpoints and definition for the MCL Cohort from Study 017001, and key aspects of the format and content of the planned sBLA dossier for R/R MCL	FDA noted subjects with relapsed/refractory MCL after at least 2 prior lines of therapy including an alkylating agent, a BTK inhibitor and CD20-targeted agent represent a population with unmet medical need FDA stated that the primary endpoint of ORR to include subjects with complete response and partial response using IRC assessments of disease response appears reasonable MCL is considered FDG-avid; therefore, FDA requires all subjects should have baseline (subjects with bridging therapy require a scan post-bridging) and post treatment PET-CT scans for accurate disease response assessment. Subjects with missing baseline PET-CT scans may not be considered evaluable for efficacy FDA stated that the subjects who are deemed to have a complete response to therapy by imaging criteria must have a bone marrow examination documenting absence of disease to be considered a complete responder, if baseline bone marrow examination was positive for lymphoma involvement For discrepancy between PET and CT findings and/or clinical findings at the time of disease response assessments, FDA requires sponsor to follow agreed upon FDA algorithm used for Study 017001 DLBCL cohort FDA suggested sponsor to ensure that a minimum sample size of 60 efficacy evaluable subjects receiving the dose to be marketed is met FDA recommends that all subjects who receive study medication have a minimum of 9 months of efficacy follow-up to ensure that all evaluable subjects have at

Date	Activity and Purpose	Key FDA Feedback
		least 6 mo follow up from first response post FDA adjudication FDA required the ITT population to include all subjects who underwent leukapheresis FDA agreed Liso-cel in MCL is exempt from pediatric study requirements Sponsor's proposal to submit clinical efficacy data only from the MCL cohort in Study 017001 is acceptable. FDA recommended Sponsor to propose a confirmatory trial of liso-cel in MCL to confirm the clinical benefit of liso-cel in this setting The Sponsor's proposal to consider any subject with PR or CR per IRC post-leukapheresis as a responder for efficacy analysis irrespective of PET status prior to liso-cel administration is acceptable to FDA ITT analysis should be based on the leukapheresed population and applicable to the dose/dose range that is intended for marketing purposes, as FDA pointed out
11-Aug-2023	Type B pre-sBLA CRMTS# 15072) Meeting held to discuss a supplemental BLA submission based on the results of Study 017001 MCL cohort	The FDA discussed limitation of a single arm study, sample size and concern regarding proposed broad indication. The Sponsor discussed revising proposed broad indication to a narrow indication of R/R MCL after BTKi intended to support full approval. The FDA suggested that the Sponsor consider a later data cutoff date included in the submission for longer DOR follow-up. Safety narratives for all subjects treated with liso-cel were required by the FDA in addition to efficacy narratives for all responders.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Additional comments provided during pre-submission interactions included the following:

- MCL is considered FDG-avid; therefore, all subjects should have baseline and post-treatment PET-CT scans for accurate disease response assessment. Subjects with bridging therapy require a scan post-bridging. Subjects with missing baseline PET-CT scans may not be considered evaluable for efficacy.
- FDA noted that concordance between PET imaging and bone marrow biopsy for disease response assessment was best established for Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL) but not for other lymphoma histologies, such as MCL, as reflected in the 2014 Lugano criteria (Cheson et al. 2014). For lymphoma subtypes other than Hodgkin lymphoma and DLBCL, bone marrow examination is the standard method for disease assessment in the bone marrow. As such, subjects in this trial who are deemed to have a complete response to therapy by imaging criteria must have a bone marrow examination documenting

absence of disease to be considered a complete responder, if baseline bone marrow examination was positive for lymphoma involvement.

- Subjects with mantle cell lymphoma can have disease at extranodal sites that may not always be FDG-avid e.g., gastrointestinal tract involvement. Such subjects must have follow-up using the appropriate test to document response to therapy (e.g., gastrointestinal endoscopy).
- All subjects who receive liso-cel (irrespective of whether the subject is considered efficacy evaluable) have a minimum of 9 months of efficacy follow-up from initial response to better characterize the durability of response. Inclusion of partial response under definition of refractory disease is not acceptable. Characterization of many subjects achieving a partial response to prior therapy as "refractory" may result in a population with better prognosis than that depicted.
- The Applicant inquired about pursuing a broad indication (e.g., patients with R/R MCL including (b) (4) patients), using a single arm trial evaluating response rate this may be adequate only as an intermediate clinical benefit endpoint in support of accelerated approval. The FDA recommended a randomized trial for the proposed indication and stated that for accelerated approval based on a single arm trial, a confirmatory trial should be ongoing at time of the BLA submission. The FDA indicated that consideration for an accelerated approval for the proposed indication will be based on available therapy at the time of regulatory action.

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

4.1. Office of Compliance and Biologics Quality (OCBQ)

Bioresearch Monitoring (BIMO) inspection assignments were issued for one foreign and three domestic clinical investigators who participated in the conduct of Study JCAR017-FOL-001. The inspections did not reveal substantiative issues that impact the data submitted in this sBLA. See BIMO reviewer's memo for details.

4.2. Product Quality

Not Applicable

4.3. Devices and Companion Diagnostic Issues

Not Applicable

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

Not Applicable

6 Clinical Pharmacology

The Applicant's Position:

The PK, pharmacodynamics, and immunogenicity of liso-cel were evaluated in the MCL Cohort of Study 017001 (refer to Section 8.1.1 for study design and analysis set definitions and Section 8.1.2 for disposition and demographics).

Clinical Pharmacokinetics

Liso-cel concentration in the peripheral blood detected by qPCR exhibited a rapid expansion followed by a monophasic decline up to 28 days after infusion in both DL1S and DL2S. However, the number of subjects receiving DL1S was small (n = 6). Additionally, there was large intersubject 30his30sensit in Cmax and AUC(0-28). For both dose levels (n = 79), median Cmax, AUC(0-28), and Tmax were 29335.0 copies/µg, 288556.8 day*copies/µg and 10.0 days, respectively.

No apparent differences in qPCR PK parameters by subgroups of age (< 65 vs ≥ 65 years old), sex, race (White vs others), pre-LDC SPD status, pre-LDC LDH status, Ki67, and TP53 mutation. A potential association was observed between blastoid morphology and lower Cmax and AUC(0-28).

Persistence of liso-cel transgene in peripheral blood, defined as a transgene count greater than or equal to the LLOD (5 copies/reaction) by qPCR, was observed up to Day 730 in 6 of 17 evaluable subjects.

Clinical Pharmacodynamics

In the total Liso-cel-treated Analysis Set (N = 88), an increase in the proportion of subjects with B-cell aplasia was observed from 58% of subjects at baseline to 98% of subjects by Month 2, with over 70% maintaining B-cell cell aplasia through Month 12.

The percentage of subjects with IgG levels < 500 mg/dL increased numerically from baseline (40%) through Month 6 (68%) and remained elevated through Month 24 (64%).

For soluble factors such as SAA, GM-CSF, IFN-γ, IL-2, IL-5, and IL-6 where an increased trend after infusion was observed, peak elevation was noted at the Day 4 or 8 collections and decreased by Day 29.

Median post-infusion serum CRP increased by Day 8 from Day 1 levels. Median serum ferritin observed had a slight upward trend from Day 1 levels between Day 11 and Day 22 but was equivalent by Day 29.

Pharmacokinetics-Efficacy/Safety Relationships

PK-efficacy relationships were evaluated in 75 subjects who were in the EAS and had evaluable PK parameters, while PK safety relationships were evaluated in 79 subjects who were in the Liso-cel-treated Analysis Set and had evaluable PK parameters.

A potential relationship was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher CR rate, longer PFS and DOR per IRC. No apparent relationship was observed between transgene PK parameters and response (BOR of either CR or PR), which could be explained by the limited number of nonresponders. Results for sensitivity analyses using response assessment per FDA algorithm (described in Section 8.1.1) were generally consistent with those per IRC assessment.

A potential association was observed between higher transgene PK parameters (Cmax and AUC[0-28]) and higher incidence of any grade CRS, any grade iiNT, and grade ≥ 3 iiNT. The relationship between PK parameters and Grade ≥ 3 CRS was not assessed because the number of subjects with Grade ≥ 3 CRS (n = 1) was less than 5.

Pharmacodynamic-Safety Relationships

Pharmacodynamic-safety relationships were evaluated in subjects who were in the Liso-cel-treated Analysis Set.

Correlative analyses were performed to evaluate the relationships of baseline and peak values (ie, Cmax) of soluble biomarkers and CRP/ferritin with selective safety endpoints including CRS and iiNT. No baseline soluble biomarker levels had an association comparing any grade CRS versus no CRS, or any grade iiNT versus no iiNT, or Grade 3 or greater iiNT categories. Among the soluble biomarkers, peak values of SAA, GM-CSF, IFN-γ, IL-2, IL-4, IL-5, and IL-6 were associated with any grade CRS versus no CRS, while only IL-2 was associated with any grade iiNT versus no iiNT. There was no association of baseline CRP or ferritin with any grade CRS, any grade iiNT, nor with Grade 3 or higher iiNT. There was an association of peak CRP but not ferritin levels with any grade CRS status. Additionally, there was no association of peak CRP or ferritin levels with iiNT status.

The number of 31his31sets with Grade ≥ 3 CRS (N = 1) was insufficient to assess a

relationship in both the DL1S and DL2S cohorts, respectively.

Immunogenicity

The incidence and prevalence of ATA were 17.6% (15 of 85 subjects) and 12.6% (11 of 87 subjects), respectively.

Due to the small number of subjects who had pre-existing ATA or treatment induced ATA, the relationship between ATA status and efficacy, safety, or PK was not conclusive.

Rationale for Dosing Regimen Selection in Study 017001

Initially for dose-finding in the MCL cohort, eligible subjects were assigned to receive a liso-cel dose of 50 × 10^6 CAR+ T cells (DL1S) that when converted to weight-based doses was similar to the range of generally well-tolerated and active doses for SCRI CD19v1, another CAR T cell product using the same CAR construct, transgene, and lentiviral vector as liso-cel.[35] A dose regimen was allowed to graduate from the dose-finding phase of the study to the dose-expansion phase for further safety and efficacy evaluation if it met early success criteria for enrollment suspension.

The following single-dose regimens were evaluated during the dose-finding phase:

- Dose Level 1 (**DL1S**): 50 × 10^6 CAR+ T cells single-dose regimen
- Dose Level 2 (**DL2S**): 100 × 10^6 CAR+ T cells single-dose regimen

Based on the cumulative efficacy and safety data from the dose-finding and dose-expansion phases of the study, in consultation with the SC, a recommended regimen for the MCL Cohort of 100 × 10^6 CAR+ T cells (DL2S) was selected. The study enrolled subjects at this regimen for further testing in the dose confirmation group. A total of 77 out of 83 subjects in the EAS and a total of 82 out of 88 subjects in the Liso-cel-treated Analysis Set (refer to Table 6 for analysis set definitions) were assigned to DL2S, and therefore DL2S represents the largest experience at a single dose regimen with regards to efficacy and safety in MCL.

Confirmation of the Selected Doses and Regimens in Study 017001

Clinical efficacy and safety results:

In the EAS, DL2S was associated with clinically meaningful ORR (83.1%), CR rate (72.3%) and mDOR (15.7 months) per IRC. Consistent results were observed per FDA algorithm (described in Section 8.1.1) with similar ORR (84.4%), CR rate (71.4%) and mDOR (14.5 months).

The median total liso-cel dose infused was 99.5 x 10^6 CAR+ T cells (range: 62 to 103 x 10^6) in the Liso-cel-treated Analysis Set (DL2S). Of the 77 subjects in the EAS (DL2S), 70 (90.9%) subjects received liso-cel in the range of 90 to 110 X 10^6 which represents ±

10% of the DL2S target dose and which is also the approved dose range in 2L LBCL. The efficacy outcomes in the EAS for those subjects receiving an administered dose in the range of 90 to 110 x 10^6 CAR+ T cells (n=70) (Table 23) are presented and are comparable to the overall EAS (n = 83) (Table 19) with similar ORR (85.7% vs 84.4%), CR rate (72.9% vs 71.4%) and median DOR (95% CI) (14.5 months [6.2, 23.3] vs 14.5 months [6.2, 23.3]) per FDA algorithm (described in Section 8.1.1).

The overall safety profile of the proposed liso-cel dose was consistent with that previously observed in 3L+ and 2L LBCL and is considered acceptable in the context of the observed clinical efficacy.

The proposed liso-cel dose range of 90 to 110 x 10^6 CAR+ T cells for the USPI is consistent with the DL2S dose studied in Study 017001 MCL cohort and with the approved dose range in 2L LBCL.

PK/Pharmacodynamics:

Results from the PK/pharmacodynamic analyses in the MCL Cohort of Study 017001 demonstrated the established benefit-risk profile that remains unaffected by liso-cel exposure at the proposed target dose.

The FDA's Assessment:

Refer to the clinical pharmacology review memo for information related to the FDA review of pharmacokinetics/pharmacodynamics parameters and dosing considerations. This trial first evaluated lower doses in the dose finding portion of the study (i.e., 50 × 10^6 CAR+ T cells). Following the dose finding and expansion phases, the committee recommended a dose regimen of 100 × 10^6 CAR+ T cells (dose level 2; DL2S) ±20% which resulted in a dose range of 79.5 to 120.5 x 10^6 cells. However, the Applicant's proposed commercial dose is 90 to 110 × 10^6 CAR+ T cells. The rationale for the proposed recommended dose selection is provided above. Though responses were observed at doses lower than the proposed commercial doses, the FDA clinical pharmacology team agreed with the Applicant's proposed dose. Subjects who received less than 90 × 10^6 were not included in the primary efficacy analysis.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 3: Applicant – Listing of Clinical Trials Relevant to this sBLA

Trial Identity NCT no. No. of Countries and Sites	Trial Design *Primary Endpoint(s)*	Description of Study Population	Regimen/ schedule/ route	Study Status No. Liso-cel Treated[a]	Data Cut
Pivotal Study in 3L+ MCL					
Study 017001 (TRANSCEND NHL-001) NCT02631044 Countries: 1 (US) Sites: 14	Phase 1, open-label, single-arm, multicohort liso-cel monotherapy *Safety and ORR per IRC*	Adult male and female subjects with R/R B-cell NHL with MCL histology after at least 2 prior lines of systemic MCL therapy.	Liso-cel was infused on Day 1 at a dose of 50 x 10^6 (DL1) or 100 x 10^6 (DL2) CAR+ T-cells, 2 to 7 days after completion of LDC	Ongoing 88 (MCL Cohort)	19-Jan-2023 (sBLA) 23-May-2023 (efficacy)
Hematologic Malignancies Supportive Studies (Included in the Liso-cel Monotherapy Pool)					
017001 (TRANSCEND NHL-001) NCT02631044 Countries: 1 (US) Sites: 14	Phase 1, open-label, single-arm multi cohort liso-cel monotherapy *Safety and ORR per IRC*	3L+ CD19+ large B-cell lymphoma (DLBCL NOS including transformed indolent NHL, HGL, FL3B, PMBCL)	DL1: 50 × 10^6 DL2: 100 × 10^6 DL3: 150 × 10^6	Ongoing DLBCL: 268	DLBCL: 12-Apr-2019 (BLA)
JCAR017-BCM-003 (TRANSFORM) NCT03575351 Countries: 11 Sites: 53	Phase 3, randomized, open-label, parallel group, controlled monotherapy. *EFS per IRC*	2L TE CD19+ large B-cell lymphoma (DLBCL NOS Including transformed indolent NHL, HGL, FL3B, PMBCL, THRBCL)	Liso-cel was infused on Day 29 at a single dose of 100 × 10^6 CAR+ T-cells, 2 to 7 days after completion of LDC.	Ongoing Arm B: 89	08-Mar-2021 (sBLA)

Trial Identity **NCT no.** **No. of Countries and Sites**	**Trial Design** ***Primary Endpoint(s)***	**Description of Study Population**	**Regimen/ schedule/ route**	**Study Status** **No. Liso-cel Treated[a]**	**Data Cut**
017006 (TRANSCEND-NHL-006/ PILOT) NCT03483103 Countries: 1 (US) Sites: 23	Phase 2, open-label, single-arm liso-cel monotherapy *ORR per IRC*	2L TNE CD19+ large B-cell lymphoma (DLBCL NOS including transformed follicular lymphoma, HGL, FL3B)	Liso-cel was infused on Day 1 at a single dose of 100×10^6 CAR+ T-cells, 2 to 7 days after completion of LDC.	Ongoing 61	28-May-2021 (sBLA)
GC-LTFU-001; non-interventional Countries: 13 Sites: 62	Non-interventional *Safety*	All subjects treated with a CAR+ T-cell therapy in a Company sponsored study, including liso-cel	NA	Ongoing 205[b]	31-Jan-2023

[a] Number of subjects treated with liso-cel product as of the data cutoff date.
[b] Includes 16 subjects from MCL Cohort who entered the LTFU study as of the 19-Jan-2023 cutoff date for the sBLA.

The Applicant's Position:

Efficacy results from the prespecified primary and secondary endpoints evaluating the efficacy of liso-cel in the MCL cohort of Study 017001 provide evidence for efficacy to support the proposed indication.

The FDA's Assessment:

The endpoints were revised during the course of the trial. Amendment 3 made efficacy a primary endpoint rather than secondary. See Protocol Amendments, Section 8, Statistical and Clinical Evaluation for further details.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 017001

Trial Design

The Applicant's Description:

Study 017001 is an open-label, multicenter, Phase 1 study to evaluate the safety, antitumor activity, and PK of liso-cel in adult subjects with R/R B-cell NHL. Two disease-specific cohorts were enrolled: 1) DLBCL cohort, and 2) MCL cohort. Data from the MCL cohort is the focus of this sBLA.

Considering there is no single SOC for the treatment of patients with R/R MCL, and therefore, due to the lack of an appropriate comparator group for a randomized trial design, a single-arm study was deemed most appropriate in this population. Potential bias regarding efficacy assessments in this study was mitigated by employing an IRC for the efficacy assessments.

The study was designed as a dose-finding, dose-expansion, and dose-confirmation study (Figure 1). The dose finding groups within each cohort were designed to evaluate the dose level and schedule of liso-cel needed for adequate safety and antitumor activity. Dose expansion groups were designed to further assess the efficacy and safety of liso-cel. Consistent with the principles of seamless oncology trials design for therapies with adequate preliminary evidence of a promising benefit/risk profile, a dose confirmation group (or groups) further evaluated the safety and efficacy of liso-cel in subjects with MCL at the recommended dose level which was 100 × 10^6 CAR+ T cells.

Study 017001 was designed as a single-arm study.

Figure 1: Applicant – 017001 Study Design Schematic – MCL Cohort

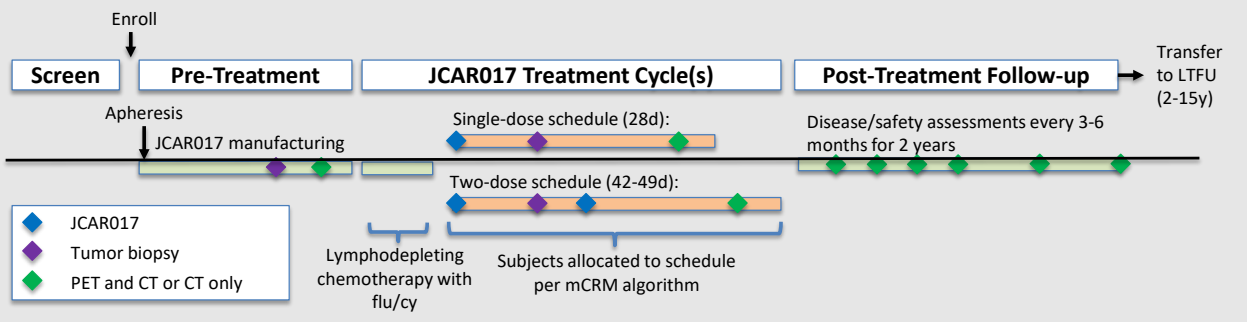


Table 4: Applicant – Study 017001 Design Details

Design Aspect	Description
Eligibility Criteria	Eligible subjects were ≥ 18 years of age and had R/R MCL after ≥ 2 lines of therapy including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent) (of note, prior to Amendment 7, subjects were required to have ≥ 1 prior line of therapy). Subjects were required to have adequate bone marrow function (as assessed by the Investigator, with no protocol-specified lower threshold for hematology parameters) to receive lymphodepleting chemotherapy, adequate organ function including CrCL >30mL/min and LVEF ≥ 40%, an ECOG PS of 0 to 1 (of note, prior to Amendment 5, subjects were required to have an ECOG PS of 0 to 2), and PET-positive disease confirmation at baseline. Subjects with secondary CNS lymphoma or prior autologous or allogeneic HSCT were allowed to enroll. Exclusion criteria included subjects with CNS-only involvement by malignancy; history of another primary malignancy that has not been in remission for at least 2 years; history or presence of clinically relevant CNS pathology; active infection, allogeneic HSCT within 90 days of leukapheresis; prior CAR-T cell or other genetically-modified T-cell therapy other than liso-cel; or evidence of graft-versus-host disease.
Trial location	14 sites in the United States.
Diagnostic criteria	MCL diagnosis had to be confirmed with cyclin D1 expression or evidence of t(11;14) by cytogenetics, FISH, or PCR.
Dose selection	See Section 6
Study treatments	Subjects were assigned to receive either 1 or 2 doses of liso-cel per treatment cycle. In the single-dose schedule, liso-cel was to be given 2 to 7 days after completion of LDC. In the 2 dose schedule, liso-cel was to be given on Day 1 (2 to 7 days after completion of LDC), and again 14 days later (ie, on Day 15). The following dose levels were planned to be evaluated: • Dose Level 1 (DL1): 50×10^6 CAR+ T cells (25×10^6 CD8+ CAR+ T cells and 25×10^6 CD4+ CAR+ T cells); single and 2-dose regimens tested: DL1S and DL1D, respectively • Dose Level 2 (DL2): 100×10^6 CAR+ T cells (50×10^6 CD8+ CAR+ T cells and 50×10^6 CD4+ CAR+ T cells); single-dose regimen only: DL2S • Dose Level 3 (DL3): 150×10^6 CAR+ T cells (75×10^6 CD8+ CAR+ T cells and 75×10^6 CD4+ CAR+ T cells); single-dose regimen only: DL3S
Assignment to treatment	For the MCL cohort, the following single-dose regimens were evaluated during the dose-finding phase: • Dose Level 1 (DL1S): 50×10^6 CAR+ T cells single-dose regimen • Dose Level 2 (DL2S): 100×10^6 CAR+ T cells single-dose regimen Opening of the dose-finding group of DL3S was not done due to the encouraging findings in the dose-finding and dose-expansion groups of DL2S
Administrative structure	A SC, comprising at least 2 Pis and the Sponsor's medical director and statistician, oversaw the conduct and scientific validity and integrity of the study. An SRC, comprising Principal Investigators and the Sponsor's Medical Monitor, statistician, and safety physician, regularly assessed the safety of liso-cel administration throughout the trial. An independent DSMB reviewed cumulative data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the study.

Design Aspect	Description
	An IRC reviewed radiographic and pertinent clinical data and determined response and progression status for subjects. Clinical management of study subjects was based upon investigator assessment.
Concomitant medications	Per study design, acetaminophen and diphenhydramine hydrochloride (or equivalent PO or IV antihistamine) were recommended as premedication before liso-cel to minimize the risk of IRR. In addition, specific concomitant medications were used for the treatment of CRS as well as neurological toxicities as detailed in the protocol.
Treatment compliance	Monitored by drug accountability, as well as subject's medical record and eCRF.
Subject completion, discontinuation, or withdrawal	In the Post-treatment Follow-up phase, subjects were followed for 2 years for safety, disease status, additional anticancer therapies, and survival. Upon completion of this study, subjects were asked to enroll in a long-term follow-up study (GC-LTFU-001), and followed for up to 15 years for survival, long-term toxicity, and viral vector safety.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of the trial design and the Applicant's statement that potential bias regarding efficacy assessments in this single-arm, open-label study was mitigated by employing an IRC for the efficacy assessments.

The FDA agrees with the Applicant's description of the Study 017001 MCL cohort, the study schema, and key eligibility criteria; however, the FDA notes that during the course of the trial there were eight protocol amendments, including revisions to key eligibility criteria (e.g., line of therapy, ECOG PS), and five revisions to the statistical analysis plan (SAP). There were revisions to the definition of the MCL primary analysis set (PAS), study duration, timing of analysis, statistical methods, sample size, and power calculations. For example, initially subjects were required to have received at least one prior line of therapy, but this was subsequently updated to specify that subjects must have failed two lines of prior systemic therapy and have been treated with an alkylating agent, BTKi, or rituximab (or other CD20-targeted agent). Additionally, Amendment 5 excluded further enrollment of subjects with ECOG PS of 2 because of the lack of benefit patients with ECOG PS 2 subjects were receiving from JCAR017 across several NHL histologies; these subjects were subsequently excluded from the PAS.

The FDA agrees with the Applicant's recommended dose of 100×10^6 CAR+ T cells but notes that responses were also observed at lower dose levels (refer to clinical pharmacology review for more details).

BREYANZI was administered in the inpatient (85%) and outpatient (15%) settings.

Upon completion of this study, subjects were asked to enroll in a long-term follow-up study; however, the majority of subjects did not consent to the 15-year follow-up or died precluding longer term follow-up.

Study Endpoints

The Applicant's Description:

The efficacy endpoints in this study were standard measures commonly used in oncology clinical trials. All secondary endpoints are considered valid assessments of efficacy in subjects with MCL. CR rate was a key secondary endpoint included in the hierarchical testing procedure for the study (see Statistical Analysis Plan subsection below).

Table 5: Applicant – Study 017001 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety of liso-cel in adult subjects with R/R B-cell NHL	Type, frequency, and severity of Aes and laboratory abnormalities. Probability of DLT estimated by the modified continual reassessment method.
To assess the antitumor activity of liso-cel	ORR, defined as the proportion of subjects with a BOR of either CR or PR per IRC assessment of disease status as determined by CT and PET (based on Lugano 2014 criteria[36]) from the time of the final liso-cel infusion of the initial cycle until disease progression, EOS, the start of another anticancer therapy, or HSCT
Secondary	
To assess the rate of CR and durability of antitumor activity of liso-cel	CR rate, defined as the proportion of subjects with BOR of CR per IRC based on Lugano 2014 criteria,[36] from the time of the final liso-cel infusion of the initial cycle until disease progression, EOS, the start of another anticancer therapy, or HSCT DOR, defined as the time from first response (CR/PR) to earlier date of PD or death
To estimate the PFS and OS of subjects treated with liso-cel	PFS, defined as the time from first infusion of liso-cel to PD or death PFS ratio, defined as the ratio of PFS to the most recent line of therapy prior to liso-cel to the PFS on liso-cel OS, defined as the time from treatment with liso-cel to the date of death
To characterize the PK profile of liso-cel	Cmax, Tmax, AUC, and other relevant PK parameters of liso-cel in blood
To assess HRQoL and HEOR	Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and the EuroQol instrument EQ-5D-5L. Numbers of ICU inpatient days and non-ICU inpatient days and reasons for hospitalization
Exploratory	
To assess the effect of liso-cel on antitumor activity using Bayesian methods	A mCRM was used to estimate the probability of CR based on investigator assessments to determine the dose assignment of the next subject.
To assess immune responses to liso-cel	Immune responses to liso-cel were evaluated with a validated ATA assay to detect the presence of plasma antibodies that bind to the extracellular region of liso-cel.
To assess the PD effects of liso-cel	Measurement of B cell numbers, plasma cytokines and chemokines, and changes in tumor and tumor microenvironment factors including, but not limited to, presence of T cell subsets and expression of tumor immune checkpoint markers

Objectives	Endpoints
To assess the effect of liso-cel attributes on safety, PK, and antitumor activity	Liso-cel product characteristics (e.g., T cell subsets, transduction efficiency, immunophenotype and gene expression at time of administration and post-dose)
To assess the effect of tumor and tumor microenvironment on liso-cel PK and pharmacodynamics	Evaluation of tumor biopsies for CD19 expression and attributes of tumor and tumor microenvironment, including, but not limited to, the presence of T cell subsets and expression of tumor immune checkpoint markers

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary efficacy (ORR) and secondary endpoints, as outlined in the most recent protocol version (Amendment 8). ORR is an endpoint reasonably likely to predict clinical benefit. ORR is typically considered an intermediate clinical endpoint whose correlation with other established endpoints such as progression-free survival (PFS) or overall survival (OS) may be unclear. FDA has also considered ORR as assessed by an IRC that is high in magnitude, durable, and with a high proportion of complete responses to be a direct measure of clinical benefit. Time-to-event endpoints such as the secondary endpoints PFS and OS, are uninterpretable in single-arm trials.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Sets

Efficacy analysis used the PAS, EAS, and ITT analysis sets. Safety analysis used the Liso-cel-treated Analysis Set.

Table 6: Applicant – Analysis Set Definitions

Analysis Population	Dose Level(s) and Grouping	Purpose
Leukapheresed Analysis Set (ITT): all subjects who signed informed consent, who met all inclusion/exclusion criteria, and underwent leukapheresis	Total (DL1S and DL2S)	Efficacy presentation
	DL2S	Efficacy and USPI presentation
Liso-cel-treated Analysis Set: All subjects who have received at least one dose of conforming liso-cel cell product.	Total (DL1S and DL2S)	Safety and USPI presentation

Analysis Population	Dose Level(s) and Grouping	Purpose
Liso-cel-treated Efficacy Analysis Set (EAS): All subjects in Liso-cel-treated Analysis Set who have PET-positive disease present before liso-cel administration per IRC. Those without baseline disease assessment after anticancer therapy for disease control and before liso-cel administration were excluded.	Total (DL1S and DL2S)	Efficacy presentation
	DL2S 90 to 110 × 10^6 CAR+ T cell dose range	Efficacy and USPI presentation
Primary Analysis Set (PAS): All subjects in the Liso-cel-treated Efficacy Analysis who met all of the following: -PET-positive disease at baseline per IRC assessment -Failed at least 2 prior lines of systemic therapy including an alkylating agent, a BTKi, and rituximab (or other CD20-targeted agent) -Received the recommended dose regimen (ie, DL2S)	DL2S only	Hypothesis testing

Primary Efficacy Endpoint

ORR per IRC assessment based on the Lugano 2014 criteria[36] was the primary efficacy endpoint to be tested in the PAS.

The primary efficacy analysis tested the null hypothesis of ORR ≤ 40% against the alternative hypothesis that the ORR > 40% at a 1-sided 2.5% level of significance, powered for ORR = 65%, for the PAS.

The ORR was calculated along with the 2-sided 95% exact Clopper-Pearson confidence intervals. The number and proportion of subjects who were evaluated as CR, PR, SD, non-PD, PD, or not evaluable/not done was also tabulated.

The primary analysis was planned to be carried out after at least 50 subjects in the MCL PAS had been treated with liso-cel at the recommended regimen, and these subjects had a minimum 6 months of follow-up from first response or until death, disease progression, or withdrawal from study. Based on the sample size recommendation by FDA (20 Apr 2021 Type B Meeting), the decision was prospectively made to do the primary analysis once a minimum of 70 subjects were treated at the same administered dose level with at least 6 months follow-up from the first objective response.

Key Secondary Efficacy Endpoint

If the primary hypothesis for ORR is rejected at the 1-sided 2.5% level, the study will test the hypothesis that the CR rate per IRC assessment > 18% against the null hypothesis that the CR rate ≤ 18% at the same level of significance, powered for CR rate = 40% for the PAS.

Other Secondary Endpoints

Other secondary endpoints included:

- **DOR, PFS, and OS:** analyzed using KM methodology for IRC assessment.
- **PK:** The PK analyses were based on qPCR. Noncompartmental PK parameters such as Cmax, Tmax and AUC(0-28) were calculated. Persistence was defined as a transgene count greater than or equal to the LOD of 5 copies/reaction.

- **HRQoL:** the EORTC QLQ-C30 and EQ-5D-5L were scored according to the recommendations in the scoring manuals. Absolute scores and change from Baseline scores were tabulated (number, mean, standard deviation, median, Q1/Q3, Min/Max, and p values for change from Baseline) at each time point. Within-patient change was evaluated with the proportion of patients with meaningful improvement, no meaningful change, and meaningful deterioration over time.
- **HRU:** hospital resource utilization was assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Descriptive statistics of ICU inpatient days and non-ICU inpatient days will be provided for subjects in the PAS.

Sensitivity Analyses

Sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CR rate, DOR, PFS, and OS, were performed based on (1) the Leukapheresed (ITT) Set using IRC assessment and (2) the EAS using investigator assessment.

FDA Algorithm

In accordance with feedback received from the FDA at the Type B meeting (20-Apr-2021), sensitivity analyses of the primary (ORR) and secondary efficacy endpoints (CR rate, DOR, and PFS) were also performed. These sensitivity analyses, hereafter referred to as the "FDA algorithm," were based on the integration of CT scan-determined PD and clinical PD as follows:

1) The following scenarios were categorized as PD regardless of PET-based metabolic response at that time point:
   a. Complete metabolic response/partial metabolic response on PET and disease progression on CT scan
   b. Stable metabolic disease on PET and disease progression on CT scan
   c. New lesion on CT scan regardless of whether the new lesion is fluorodeoxyglucose avid on PET
   d. Clinical (non-radiographic) PD per investigator

   In addition, spleen measurements were incorporated into the CT scan radiology assessments.
2) BMB was required to confirm a CR for subjects who either:
   a. Had evidence of baseline bone marrow lymphoma involvement based on the BMB or PET scan performed closest to LDC, or
   b. Had no evidence of baseline bone marrow lymphoma involvement prior to LDC infusion based on a PET scan, and did not have a baseline BMB performed, and had delayed recovery of prolonged cytopenia, defined as laboratory-based Grade ≥ 3 anemia, neutropenia, or thrombocytopenia at the Day 29 visit that did not resolve to Grade ≤ 2 on or before the Day 90 visit.

   For the MCL subjects that met one of the criteria above, the CR was to be downgraded to PR if the post baseline bone marrow biopsy data was positive or missing.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the endpoints as described in the study protocol and CSR. The FDA's primary efficacy assessment was not based on the Applicant's described primary analysis set (PAS). Rather, the FDA review team based the efficacy analysis on the subset of patients who received at least 2 prior lines of therapy including an alkylating agent, BTKi, a CD20-targeted agent, had PET evaluable disease at baseline (and after bridging therapy, as applicable) and received conforming product at the proposed marketing dose of 90 to 110 × 10^6 CAR+ T cells.

FDA's primary efficacy review was based on Lugano 2014 criteria (Cheson et al. 2014). As noted by the Applicant as 'FDA algorithm', the FDA's analysis additionally took into consideration CT and/or clinical evidence of progressive disease and bone marrow assessment (as described below) in adjudication of disease response:

1) The following scenarios were categorized as PD regardless of PET-based metabolic response at that time point:

   c) Complete metabolic response/partial metabolic response on PET and disease progression on CT scan
   d) Stable metabolic disease on PET and disease progression on CT scan
   e) New lesion on CT scan regardless of whether the new lesion is fluorodeoxyglucose avid on PET
   f) Clinical (non-radiographic) PD per investigator

   In addition, spleen measurements were incorporated into the CT scan radiology assessments.

2) Downgrades from CR to PR was based on FDA adjudication using Lugano 2014 criteria (Cheson et al. 2014) which suggests a bone marrow biopsy should be obtained as there are inadequate data to support the use of PET FDG to assess bone marrow involvement in histologies other than Hodgkin Lymphoma and LBCL. As such, a BMB was required to confirm a CR for subjects who either:

   a) Had evidence of baseline bone marrow lymphoma involvement based on the BMB or PET scan performed closest to LDC, or
   b) Had no evidence of baseline bone marrow lymphoma involvement prior to LDC infusion based on a PET scan, and did not have a baseline BMB performed, and had delayed recovery of prolonged cytopenia, defined as laboratory-based Grade ≥ 3 anemia, neutropenia, or thrombocytopenia at the Day 29 visit that did not resolve to Grade ≤ 2 on or before the Day 90 visit.

Protocol Amendments

The Applicant's Description:

The original protocol for this study was dated 21-May-2015. As of the data cutoff date of 19-Jan-2023 for this addendum, 8 protocol amendments were filed during the conduct of the study.

Table 7: Applicant – Summary of Key Changes to Protocol 017001

Document (Amendment)/Date	Summary of Key Changes
Amendment 1/ 24-Sep-2015	• Corrected and completed eligibility criteria for adequate renal function • Provided additional information for continued liso-cel treatment (additional cycles) in subjects who achieve a response following liso-cel therapy (Note, the option for additional cycles was removed in Amendment 6) • Provided additional dosing recommendations for administration of LDC • Added details regarding number of subjects enrolled in the regimen-finding portion of the study, the number of subjects within each disease cohort, and the number of subjects that may be added to a given dose regimen for further evaluation • Updated the simulation report to include the hierarchical dose-response model, simulation results, and model operating characteristics by borrowing efficacy data across disease cohorts
Amendment 2/ 14-Mar-2016	• A second group of subjects may be enrolled and treated at a higher dose of liso-cel (100×10^6 CAR+ T cells) on the single- and 2 dose schedules if acceptable safety is observed among at least 6 subjects treated with 50×10^6 CAR+ T cells (Group A) on a single-dose schedule • The planned maximum sample size was increased from 70 to 90 subjects • A separate Bayesian adaptive design simulation report for Dose Level 2 (Group B) was added
Amendment 3/ 29-Jun-2016	• Allowed for a third, higher liso-cel dose level (150×10^6 CAR+ T cells) • Allowed for expansion groups to be opened at a dose level once that level has been shown likely to be safe and efficacious during the dose-finding portion of the study • Updated the sample size of the study and other statistical methods as a result of the above changes • Made efficacy a primary endpoint rather than secondary • Added an SC to be responsible for overseeing the conduct and scientific validity and integrity of the trial, and clarified the role of the SRC • Specified that efficacy evaluations will be performed both by the investigator and by a central IRC • Lengthened the follow-up time on this study to 2 years before subjects enroll in the long term follow up study, and added appropriate evaluations for this time period • Specified that subjects must have archived tumor biopsy tissue available or, if at least one tumor-involved site is deemed accessible at time of screening, willing to undergo biopsy for disease confirmation at baseline • Added an exclusion for prior CAR T-cell or other genetically-modified T cell therapy • Clarified that steroids can be used after lack of response, subsequent therapy for lymphoma, or 1 year following liso-cel treatment • Expanded definitions of relationship to study drug. With the longer duration of this study, this change allows for long-term sequelae to be assessed more accurately

Document (Amendment)/Date	Summary of Key Changes
Amendment 4/ 05-Jan-2017	• Defined a more homogeneous PAS for efficacy analyses • Added provision for a dose confirmation group to further test the safety and efficacy at a recommended dose regimen already estimated to be safe and effective • Added chemorefractory subgroup (and an efficacy hypothesis for this subgroup for the DLBCL cohort) • Changed CR and DOR from primary to secondary endpoints, changed assessment of CR using Bayesian methods to exploratory, and added PFS ratio as a secondary endpoint • Added subgroup analyses for safety and efficacy analyses • Allowed subjects with CNS involvement of their lymphoma, and excluded subjects with CNS-only disease • Added HRQoL and HEOR as secondary objectives • Updated information regarding potential risks and management of treatment toxicities to align with the current IB, including updating the CRS management algorithm • Updated the safety reporting rules (including increasing the reporting period for all Aes from 30 to 90 days following liso-cel infusion and specifying that all AE/SAEs will be collected for 30 days following initiation of new noncytotoxic anticancer therapy) • Added guidance for administration of liso-cel in an outpatient setting when appropriate
Amendment 5/ 14-Aug-2017	• Allowed for more than 1 dose confirmation group, and added reference to stopping rules for a dose confirmation group were implemented to help detect safety and futility signals that may have occurred during the course of a dose confirmation group • Added safety and futility monitoring boundaries for dose confirmation group • Excluded further enrollment of subjects with ECOG PS of 2 at screening • Updated CRS management algorithm and guidance regarding NT based on most recent data. More specific language was added regarding actions to be taken in cases of potential CRS, especially for Grade 1 and 2 events. • Specified evaluations needed in subjects who receive leukapheresis but no treatment
Amendment 6/ 13-Apr-2018	• Implemented larger windows around the Day 180 and Day 270 PET and CT scans to allow for more flexibility in the timing of scans and allow collection of follow-up response data 6 months from first response • Added sentence to emphasize that fludarabine doses should be adjusted in subjects with renal insufficiency, in accordance with the fludarabine label • Changed the PK objective from primary to secondary • Refined CRS and NT management algorithms to be consistent with letter previously sent to sites • Added guidance regarding subject clinical stability prior to liso-cel administration • Removed the possibility of additional cycles for subjects who responded to liso-cel but did not achieve CR • Added flexibility to enrollment numbers to ensure adequate enrollment for the PAS
Amendment 7/ 19-Dec-2019	• Updated inclusion criterion to specify that subjects in MCL cohort must have failed at least 2 lines of prior systemic therapy and have been treated with an

Document (Amendment)/Date	Summary of Key Changes
	alkylating agent, Bruton's tyrosine kinase inhibitor, and rituximab (or other CD20-targeted agent) • Defined and allowed inclusion of a dose-confirmation group for the MCL cohort • Updated the definition of the MCL primary analysis set, study duration, timing of analysis, statistical methods, sample size, and power calculations
Amendment 8/ 30-Aug-2021	• Included the requirement of having a post-baseline bone marrow biopsy assessment to confirm CR in MCL subjects with a baseline bone marrow involvement by imaging or bone marrow biopsy, or a delayed recovery of prolonged cytopenia in subjects with missing baseline bone marrow biopsy

The FDA's Assessment:

The FDA agrees with the Applicant's summary of protocol amendments which included revisions in protocol eligibility, primary and secondary endpoints, and dose.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with GCP, as defined by ICH and in accordance with the ethical principles underlying EU Directive 2001/20/EC and the US CFR, Title 21, Part 50.

No GCP deviations impacting the study were reported.

(b) (4), which provided eCOA services for the study, (b) (4) that the Sponsor determined had no impact on patient safety or data integrity.

The FDA's Assessment:

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

Financial Disclosure

The Applicant's Position:

Financial interests of arrangements with clinical investigators have been disclosed (see Appendix 17.4). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the 017001 clinical study 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 financial interests with clinical investigators have been disclosed.

Financial disclosure information was provided for 420 investigators and sub-investigators, 6 of whom were noted to have disclosable financial interests. The Applicant provided a description of steps that have been taken to minimize potential bias from these reported financial interests (see section 17.4 for additional information). The review of the financial disclosures did not identify issues that could unfavorably impact the clinical review of the submission.

Patient Disposition

Data:

Table 8 : Applicant – Analysis Populations MCL

Population	DL2S	DL1S	Total
Leukapheresed Set (ITT)	94	10	104
Liso-cel-treated Analysis Set	82	6	88
Liso-cel-treated Efficacy Analysis Set (EAS)	77	6	83
Primary Analysis Set (PAS)	74	0	74

Source: ADSL.

Table 9: Applicant – Enrollment Information – Screened Set MCL

	DL2S	DL1S	Total
Subjects Screened	-	-	105
Screen Failure[a]	-	-	2 (1.9)d
Screen Success[a]	-	-	103 (98.1)
Subjects Screened Success but no Leukapheresis[a]	-	-	0
Subjects Screened and underwent Leukapheresis[a]	94 (100)	10 (100)	104 (99.0)
Not Infused/Treated with liso-cel[b]	9 (9.6)	3 (30.0)	12 (11.5)
Subject no longer meets eligibility criteria for other reasons	0	1 (33.3)	1 (8.3)
Death	6 (66.7)	2 (66.7)	8 (66.7)
Other	3 (33.3)	0	3 (25.0)
Received LDC[b]	86 (91.5)	7 (70.0)	93 (89.4)
Received product infusion[b]	85 (90.4)	7 (70.0)	92 (88.5)
Subjects who received product infusion[b]	85 (90.4)	7 (70.0)	92 (88.5)
Received nonconforming product at first infusion	3 (3.5)	1 (14.3)	4 (4.3)
Received conforming product at first infusion	82 (96.5)	6 (85.7)	88 (95.7)

[a] Percentages are based on the numbers in row of 'Subjects Screened'.
[b] Percentages are based on the number in row of 'Subjects underwent Leukapheresis'.
[d] One subject who underwent leukapheresis was retrospectively determined to have met exclusion criteria 2, regarding prior malignancies and discontinued the study prior to receiving LDC and liso-cel infusion.
Source: ADSL

The Applicant's Position:

A total of 105 subjects were screened at 14 sites in the US. 104 subjects underwent leukapheresis, of whom 93 (89.4%) subjects received LDC and 92 (88.5%) subjects received CAR T cell product infusion, including 88 (95.7%) subjects who received liso-cel (82 treated at DL2S and 6 treated at DL1S) and 4 (4.3%) subjects who received

nonconforming product (defined as any product wherein a component did not meet a release specification limit required for liso-cel).
As of the 19-Jan-2023 data cutoff for the sBLA, in the Liso-cel-treated Analysis Set (N = 88), 54.5% had discontinued the study, 34.1% had completed the study, and 11.4% of subjects were ongoing in the trial. The primary reason for study discontinuation was death (50.0%). Of the 30 subjects who completed the study in the Liso-cel-treated Analysis Set, 16 consented to long-term follow-up. The median duration of study follow-up in the Liso-cel-treated Analysis Set was 16.10 months.

The FDA's assessment:

The FDA agrees with the Applicant's summary of subject disposition. The FDA notes that more than 50% of subjects were not able to complete the 24-month study period, primarily due to death (50%). See Table 10 for details regarding the disposition of the 68 patients in the primary efficacy population as adjudicated by FDA (N = 68).

Table 10: FDA Safety and Efficacy Populations- Subject Disposition

Disposition Parameter	Safety Population N=88 n (%)	Efficacy Population N=68 n (%)
Completed study	30 (34)	20 (23)
Still on study	10 (11)	9 (10)
Discontinued study	48 (54)	39 (57)
Death	44 (50)	35 (40)
Withdrew Consent	4 (5)	4 (5)

Source: FDA analysis ADSL dataset study 17001 MCL cohort

Through information requests and responses with the Applicant, the accuracy of the reporting of the number of prior therapies was confirmed and a noted error in the database was identified by the Applicant.

Error in clinical database entry: Initially, three subjects were excluded from the FDA primary analysis set because they received less than 2 prior lines of therapy; however, the Applicant subsequently noted that in fact one of these subjects did receive 2 prior lines of therapy including a BTKi as a second line of therapy but it was not reflected in the datasets (e.g., ADSL) due to an error in the site's data entry in the clinical database. More specifically, for this subject, the site reported BTKi therapy as bridging therapy instead of reporting BTKi therapy as a second line of therapy. The FDA subsequently included this subject in the primary efficacy population. Per Applicant, this error will be corrected in the clinical database and noted in the final clinical study report.

Protocol Violations/Deviations

Data:

Table 11: Applicant – Summary of Major Protocol Deviations – Liso-cel-treated Analysis Set

	DL2S N=82	DL1S N=6	Total N=88
Subjects with Major Protocol Deviations	6 (7.3)	0	6 (6.8)
Study Procedure Deviation	3 (3.7)	0	3 (3.4)
Study Treatment Deviation	2 (2.4)	0	2 (2.3)
Prohibited Medications Deviation	1 (1.2)	0	1 (1.1)
Number of subjects with			
One major protocol deviation	6 (7.3)	0	6 (6.8)

Source: ADSL and ADDV.

The Applicant's Position:

Protocol deviations were considered major protocol deviations if they met one of the following criteria: 1) negatively impacted the safety, rights, and/or welfare of the subject, 2) negatively impacted the quality or completeness of the study data, or 3) were repeated instances of non-key deviations despite retraining. None of the major protocol deviations in the Liso-cel-treated Analysis Set had an impact on subject safety or interpretation of the data.

The FDA's Assessment:

- The FDA agrees with the Applicant's assessment that no protocol deviations appeared to have an impact on safety or interpretation of the overall data. There were 537 deviations reported; the Applicant considered 6 of them to be major deviations (involving 6 different subjects) as summarized below:
  - For four subjects, the fludarabine dose was not dose reduced for decreased creatinine clearance (per Amendment 06).
  - For one subject, anticancer treatment (zanubrutinib) for disease control was given 1 day prior to JCAR017 infusion.
  - For one subject, the pre-treatment PET scan was done prior to the subject completing intervening chemotherapy (ibrutinib) between apheresis and JCAR017. This subject was not included in the efficacy analysis due to this major protocol violation (and not having received one of the protocol-required prior systemic therapies).

Table of Demographic Characteristics

Data:

Table 12: Applicant – Demographics and Baseline Characteristics- Liso-cel-treated Analysis Set

Parameter	DL2S N=82	DL1S N=6	Total N=88
Age, years [a]			

Parameter	DL2S N=82	DL1S N=6	Total N=88
N	82	6	88
Median	69.0	66.5	68.5
Min, Max	36, 86	58, 78	36, 86
Age Group, n (%)			
≥ 65 years	60 (73.2)	4 (66.7)	64 (72.7)
≥ 75 years	17 (20.7)	1 (16.7)	18 (20.5)
Sex, n (%)			
Male	62 (75.6)	5 (83.3)	67 (76.1)
Female	20 (24.4)	1 (16.7)	21 (23.9)
Race Group, n (%)			
White	71 (86.6)	6 (100)	77 (87.5)
Others: Include Other Races	8 (9.8)	0	8 (9.1)
Unknown or Missing	3 (3.7)	0	3 (3.4)
Race, n (%)			
Asian	5 (6.1)	0	5 (5.7)
Black or African American	2 (2.4)	0	2 (2.3)
Native Hawaiian or Other Pacific Islander	1 (1.2)	0	1 (1.1)
White	71 (86.6)	6 (100)	77 (87.5)
Not Reported	3 (3.7)	0	3 (3.4)
Ethnicity, n (%)			
Hispanic Or Latino	4 (4.9)	0	4 (4.5)
Screening ECOG score, n (%)[b]			
0	45 (54.9)	3 (50.0)	48 (54.5)
1	37 (45.1)	3 (50.0)	40 (45.5)
Pre-LDC ECOG score, n (%)[b]			
0	40 (48.8)	1 (16.7)	41 (46.6)
1	41 (50.0)	4 (66.7)	45 (51.1)
2	0	1 (16.7)	1 (1.1)
3[c]	1 (1.2)	0	1 (1.1)
Baseline CRP, mg/L			
n	82	5	87
Median	14.935	51.000	15.000
Min, Max	0.25, 1444.00	13.60, 91.60	0.25, 1444.00
Baseline CRP category			
< 20 mg/L	52 (63.4)	1 (20.0)	53 (60.9)
≥ 20 mg/L	30 (36.6)	4 (80.0)	34 (39.1)
Screening LVEF[d], %			
n	82	6	88
Median	60.0	60.0	60.0
Min, Max	45, 88	59, 65	45, 88
Screening LVEF category			
≥ 40 to 50%, n (%)[d]	5 (6.1)	0	5 (5.7)
≥ 50%, n (%)[d]	77 (93.9)	6 (100)	83 (94.3)
Pre-LDC CrCl [d], mL/min			
n	81	6	87
Median	79.688	85.538	79.688
Min, Max	39.93, 195.66	49.31, 138.75	39.93, 195.66
Pre-LDC CrCl category			
< 60 mL/min, n (%)[d]	17 (21.0)	2 (33.3)	19 (21.8)

Parameter	DL2S N=82	DL1S N=6	Total N=88
≥ 60 mL/min, n (%)[d]	64 (79.0)	4 (66.7)	68 (78.2)

a. Age (years)=(date of first liso-cel infusion – date of birth + 1) / 365.25 (rounded down to an integer).
b. Pre-LDC ECOG score is the most recent ECOG score prior to the start of lymphodepleting chemotherapy; Pre-liso-cel ECOG score is the most recent ECOG score post lymphodepleting chemotherapy and prior to liso-cel infusion.
c. One subject had an ECOG score of 3 pre-LDC due to disease-related symptoms, and ECOG score improved to 2 at the time of liso-cel infusion.
d. Percentages are based on number of subjects with non-missing results.
Note: Baseline is the last observation collected on or prior to the date of the first product infusion.
Source: ADSL and ADBASE.

The Applicant's Position:

The demographic and baseline characteristics of subjects in the Liso-cel-treated Analysis Set were representative of an older (median age 68.5 years, 20.5% ≥75 years old), male MCL population with relevant comorbidities. Renal function impairment prior to LDC defined as CrCl < 60 mL/min) and reduced cardiac function at screening defined as LVEF ≥ 40% to < 50% were reported in 21.8% and 5.7% of subjects, respectively.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of the liso-cel treated population. Overall, the study population is generally representative of the MCL population as described in 2.1, although the proportion of participants who are non-Hispanic Black in the trial is numerically smaller than the 4-5% reported in the literature. The demographic and baseline characteristics were similar for the primary efficacy analysis as noted below in Table 13. The Applicant notes that Study 017001 MCL Cohort did not have a diversity plan since this study was initiated and fully enrolled prior to publication of the FDA Draft Guidance "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials - Guidance for Industry" dated April 2022.

Table 13: FDA - Demographics and Baseline Characteristics- Primary Efficacy Analysis Set (N=68)

Demographic Parameter	n (%)
Pooled age group 1	-
<65 years	19 (28)
≥65 years	49 (72)
Pooled age group 3	-
<75 years	55 (81)
≥75 years	13 (19)
Sex	-
F	17 (25)
M	51 (75)
Race	-
Asian	4 (6)
Black or African American	1 (1.5)
Native Hawaiian or Other Pacific Islander	1 (15)
White	59 (91)
Ethnicity	-
Hispanic or Latino	5 (6)
Not Hispanic or Latino	62 (91)
Unknown	2 (3)

Source: FDA review of ADSL dataset from Study 017001 MCL Cohort
Abbreviations: F, female; M, male; USPI, United States Prescribing Information.

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

Data:

Table 14: Applicant – Summary of Disease Characteristics – Liso-cel-treated Analysis Set

	DL2S N=82	DL1S N=6	Total N=88
LDH prior to LDC, U/L			
N	82	6	88
Median	229.0	465.0	233.5
Min, Max	78, 4651	164, 811	78, 4651
LDH prior to LDC category, n (%)			
≥500 U/L, n (%)[a]	7 (8.5)	3 (50.0)	10 (11.4)
<500 U/L, n (%)[a]	75 (91.5)	3 (50.0)	78 (88.6)
SPD per IRC prior to LDC, cm^2			
N	75	5	80
Median	11.960	25.300	13.855
Min, Max	0.66, 93.79	23.14, 67.26	0.66, 93.79
SPD per IRC prior to LDC category, n (%)			
≥50 cm^2 (%)[a]	5 (6.7)	2 (40.0)	7 (8.8)
<50 cm^2 (%)[a]	70 (93.3)	3 (60.0)	73 (91.3)
Ki67 proliferation fraction			
N	75	6	81
Median	60.00	52.50	60.00
Min, Max	5.0, 95.0	10.0, 75.0	5.0, 95.0

	DL2S N=82	DL1S N=6	Total N=88
Ki67 proliferation fraction category, n (%)			
≥ 30%	62 (75.6)	4 (66.7)	66 (75.0)
< 30%	13 (15.9)	2 (33.3)	15 (17.0)
TP53 mutation			
Yes	19 (23.2)	1 (16.7)	20 (22.7)
No	33 (40.2)	1 (16.7)	34 (38.6)
Indeterminate	4 (4.9)	0	4 (4.5)
Not Done	26 (31.7)	4 (66.7)	30 (34.1)
Blastoid morphology			
Yes	22 (26.8)	5 (83.3)	27 (30.7)
No	47 (57.3)	1 (16.7)	48 (54.5)
Not Done	13 (15.9)	0	13 (14.8)
Complex karyotype			
Yes	24 (29.3)	2 (33.3)	26 (29.5)
No	33 (40.2)	2 (33.3)	35 (39.8)
Indeterminate	4 (4.9)	0	4 (4.5)
Not Done	21 (25.6)	2 (33.3)	23 (26.1)
Refractory or Relapsed to last prior therapy, n (%)[b]			
Refractory	56 (68.3)	5 (83.3)	61 (69.3)
Relapsed	26 (31.7)	1 (16.7)	27 (30.7)
Prior BTKi	77 (93.9)	6 (100)	83 (94.3)
Refractory to prior BTKi[b]	43 (52.4)	4 (66.7)	47 (53.4)
Prior ibrutinib	59 (72.0)	6 (100)	65 (73.9)
Refractory to prior ibrutinib[b]	31 (37.8)	4 (66.7)	35 (39.8)
Prior venetoclax	23 (28.0)	0	23 (26.1)
Refractory to prior venetoclax[b]	17 (20.7)	0	17 (19.3)
Prior alkylator	82 (100)	6 (100)	88 (100)
Prior bendamustine	51 (62.2)	4 (66.7)	55 (62.5)
Prior anthracycline	60 (73.2)	5 (83.3)	65 (73.9)
Chemorefractory or chemosensitive[c], n (%)			
Chemorefractory	21 (25.6)	4 (66.7)	25 (28.4)
Relapse < 12 m after ASCT	0	0	0
Last Chemo	21 (25.6)	4 (66.7)	25 (28.4)
Chemosensitive	61 (74.4)	2 (33.3)	63 (71.6)
Active CNS disease at first liso-cel infusion			
Yes	7 (8.5)	0	7 (8.0)
No	75 (91.5)	6 (100)	81 (92.0)
Best prior response to any prior therapy			
Complete Response	67 (81.7)	4 (66.7)	71 (80.7)
Partial Response	10 (12.2)	2 (33.3)	12 (13.6)
Stable Disease	2 (2.4)	0	2 (2.3)
Progressive Disease	3 (3.7)	0	3 (3.4)
Months from eligible diagnosis[d] to first liso-cel infusion			
N	82	6	88
Median	65.50	48.65	63.75

	DL2S N=82	DL1S N=6	Total N=88
Min, Max	3.9, 299.5	16.8, 85.3	3.9, 299.5

[a] Percentages are based on number of subjects with non-missing results.
[b] Relapsed vs refractory is defined as best response of CR vs best response of PR, SD, or PD to last systemic or transplant treatment with curative intent. Determined by response to the CRF question "Was disease relapsed or refractory to last therapy?". Refractory to prior BTKi, ibrutinib, or venetoclax defined as any response to prior BTKi, ibrutinib, or venetoclax is less than PR.
[c] Chemorefractory is defined as experiencing SD or PD to last chemo-containing regimen or relapsed < 12 months after ASCT; otherwise, it is chemosensitive.5454
[d] Eligible diagnosis defined as subject's MCL diagnosis which met eligibility for the clinical trial.
Source: ADSL and ADBASE

Table 15: Applicant – Summary of Prior Treatments – Liso-cel-treated Analysis Set

	DL2S N=82	DL1S N=6	Total N=88
Prior Treatment, n (%)[a]			
Hematopoietic stem cell transplant	27 (32.9)	2 (33.3)	29 (33.0)
Allogeneic	5 (6.1)	1 (16.7)	6 (6.8)
Autologous	24 (29.3)	2 (33.3)	26 (29.5)
Radiotherapy	23 (28.0)	1 (16.7)	24 (27.3)
Systemic treatment	82 (100)	6 (100)	88 (100)
Number of prior systemic treatments[b]			
N	82	6	88
Mean (StD)	3.7 (1.98)	4.0 (1.41)	3.7 (1.94)
Median	3.0	4.0	3.0
Min, Max	1, 11	2, 6	1, 11
Number of prior systemic treatments,[b] n(%)			
1 prior regimen	3 (3.7)	0	3 (3.4)
2 prior regimens	27 (32.9)	1 (16.7)	28 (31.8)
3 prior regimens	18 (22.0)	1 (16.7)	19 (21.6)
4 prior regimens	10 (12.2)	2 (33.3)	12 (13.6)
≥5 prior regimens	24 (29.3)	2 (33.3)	26 (29.5)

[a] Only regimens post diagnosis of MCL are included. Bridging anticancer therapy for disease control was not counted as a prior systemic regimen unless the outcome was complete response.
[b] HSCT was not included as systemic therapy.
Source: ADSL, ADBASE and ADCM.

The Applicant's Position:

In the Liso-cel-treated Analysis Set

- The majority of subjects had at least one high risk feature (e.g., ≥ 30% Ki67 proliferation fraction, TP53 mutation, blastoid morphology, complex karyotype) and the majority (69.3%) of all subjects were refractory to their most recent prior treatment, indicating a patient population with poor prognosis and advanced disease; 8.0% of the subjects had active CNS disease at time of liso-cel infusion.
- The median number of prior systemic therapies was 3.0 (range: 1 to 11), with 29.5% of subjects having had 5 or more prior lines of therapy, reflective of a heavily

pretreated R/R population (of note, prior to Amendment 7, subjects were required to have ≥ 1 prior line of therapy).
  - The majority of subjects in the Liso-cel-treated Analysis Set (94.3%) received prior BTKi with 53.4% being refractory to BTKi.
  - All subjects received a prior alkylating agent, including bendamustine in 62.5%; 73.9% had received prior anthracycline; and 33% had received HSCT, including prior allogeneic HSCT in 6.8%.
  - 69.3% of subjects were refractory to their most recent prior treatment, indicating a patient population with poor prognosis and advanced disease
- The majority of the subjects (65.9%) received optional bridging therapy for disease control prior to LDC, indicating a population with aggressive disease.

Demographics, baseline disease characteristics, prior treatments, and rates of optional bridging therapy in the Liso-cel-treated Analysis Set were similar to those in the Leukapheresed Analysis Set (ITT).

The FDA's Assessment:

The FDA agrees with the Applicant's summary of subject baseline disease characteristics for the liso-cel-treated population (N=88) and provides below the baseline characteristics for the primary efficacy population (i.e., limited to subjects who received at least 2 prior lines of therapy and received the intended dose of 90 to 110 × 10^6 cells). The FDA notes the different definitions for refractory disease in outlined in footnotes b and c of Table 14 (e.g., refractory defined as best response of PR, SD, or PD to last systemic or transplant treatment with curative intent).

The summary of disease characteristics table below describes the FDA primary efficacy population for the proposed indication.

Table 16: FDA - Summary of Disease Characteristics - Final Efficacy Population

Characteristics	N=68 n (%)
Complex karyotype present	-
Indeterminate	4 (6)
No	28 (41)
Not Done	15 (22)
Yes	21 (31)
TP53 mutation present	-
Indeterminate	2 (3)
No	29 (43)
Not done	20 (29)
Yes	17 (25)
Blastoid morphology detected	-
No	39 (57)
Not Done	9 (13)
Yes	20 (29)

Ki67 proliferation fraction (%)	-
<30%	11 (16)
≥30%	52 (76)
Prior alkylator	68 (100)
Refractory to prior alkylator[a]	18 (26)
Prior anthracycline	50 (74)
Refractory to prior anthracycline[a]	8 (12)
Prior bendamustine	-
Refractory to prior bendamustine[a]	11 (16)
Prior BTKi exposure	68 (100)
Refractory to BTKi[a]	38 (56)
Prior ibrutinib exposure	50 (74)
Refractory to Ibrutinib[a]	27 (40)
Chemorefractory or chemosensitive disease type[b]	
Chemorefractory	18 (26)
Chemosensitive	50 (74)
Disease relapsed or refractory to last therapy[c]	-
Refractory	47 (69)
Relapsed	21 (31)
Active CNS disease	7 (10)

Source: FDA Analysis ADSL, ADBASE dataset from study 017001 MCL cohort.
[a.] Relapsed vs refractory is defined as best response of CR vs best response of PR, SD, or PD to last systemic or transplant treatment with curative intent. Determined by response to the CRF question "Was disease relapsed or refractory to last therapy?". Refractory to prior BTKi, ibrutinib, or venetoclax defined as any response to prior BTKi, ibrutinib, or venetoclax is less than PR.
[b.] Chemorefractory is defined as experiencing SD or PD to last chemo-containing regimen or relapsed < 12 months after ASCT; otherwise, it is chemosensitive.5656
[c.] Eligible diagnosis defined as subject's MCL diagnosis which met eligibility for the clinical trial.
Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; CNS, central nervous system.

Table 17: FDA – Summary of Prior Treatments – Efficacy Analysis Set

Characteristics	**N=68 n (%)**
Number of prior systemic treatments footnote[a]	-
Median (range)	3 (2,11)
2 prior regimens	23 (34)
3 prior regimens	15 (22)
4 prior regimens	8 (12)
≥5 prior regimens	21 (31)
Disease relapsed or refractory to last therapy[b]	-
Refractory	47 (69)
Relapsed	21 (31)
Hematopoietic stem cell transplant type[b]	-
Allogeneic Hematopoietic Stem Cell Transplant	2 (3)
Autologous Hematopoietic Stem Cell Transplant	18 (26)
Both	2 (3)
None	46 (68)
Bridging Therapy	44 (65)

Source: FDA Analysis ADSL, ADBASE dataset from study 017001 MCL cohort
[a] Only regimens post diagnosis of MCL are included. Bridging anticancer therapy for disease control was not counted as a prior systemic regimen unless the outcome was complete response.
[b] HSCT was not included as systemic therapy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

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.

- All (100%) subjects in the Liso-cel-treated Analysis set received at least 1 concomitant medication. The most frequently (≥ 80%) reported concomitant medications were paracetamol, diphenhydramine, and ondansetron. (Paracetamol and diphenhydramine were recommended per protocol as premedication for liso-cel to minimize the risk of infusion reactions.)
- The use of systemic antibacterial, antifungal, and antiviral agents for infection prophylaxis were also frequently reported.

The Applicant's Position:

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

The FDA's Assessment:

The FDA agrees with the Applicant's summary. Of note, steroids were permitted for management of severe CRS. The protocol did not specify allowable dose or duration of steroids.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 18: Applicant – Results of the Primary Analysis in the Statistical Testing Hierarchy – PAS

	Rate (95% CI)	Null Hypothesis/ Significance Test Level	P-Value	Statistically Significant[a]
Primary Objective: IRC-assessed ORR	86.5% (76.5, 93.3)	≤ 40% 1-sided 0.025	<0.0001	Yes

[a] 2-sided 95% exact Clopper-Pearson confidence intervals.
Source: ADSL and ADEFFSUM.

Table 19: Applicant – Analyses of ORR in the Liso-cel-treated Efficacy Analysis Set and Leukapheresed Set (ITT) per IRC and per the FDA Algorithm

	EAS		Leukapheresed Set (ITT)	
	Per IRC N = 83	Per FDA Algorithm N = 83	Per IRC N = 104	Per FDA Algorithm N = 104
ORR, n (%)				
CR+PR	69 (83.1)	67 (80.7)	73 (70.2)	71 (68.3)
95% CI [a]	(73.3, 90.5)	(70.6, 88.6)	60.4, 78.8	58.4, 77.1

[a] **2-sided 95% exact Clopper-Pearson confidence intervals.**
Note: FDA algorithm and ITT analyses are sensitivity analyses**.**

Source: ADSL, ADEFFSUM, ADSUBGRP and ADTTEE.

The Applicant's Position:

To assess efficacy of liso-cel in a homogeneous study population, hypothesis testing was conducted on the PAS for the primary analysis. To evaluate the totality of data in all R/R MCL subjects treated with liso-cel, efficacy outcomes were evaluated in the EAS.

- The primary endpoint (ORR per IRC) in the prespecified statistical testing hierarchy was met, with statistically and clinically meaningful responses to treatment in the PAS (Table 18).
- A similar high ORR of 83.1% was observed in the EAS per IRC which was consistent with the primary analysis in the PAS, as was the sensitivity analysis per the FDA algorithm (Table 19).
- Investigator-assessed ORR in the EAS (83.1% [95% CI: 73.3, 90.5]) was consistent with IRC assessment, suggesting a low impact of bias, disease heterogeneity, and evaluation variability among assessors.
- In the Leukapheresed Set (ITT), IRC-assessed ORR was numerically lower than in the PAS and in the EAS; this is an expected finding given the ITT Set comprised all subjects who underwent leukapheresis, including subjects who did not receive liso-cel (n = 12) or who received nonconforming product (n = 4) (Table 9). Sensitivity analyses of ORR using the FDA algorithm yielded results consistent with those obtained by IRC assessment (Table 19).

The FDA's Assessment:

FDA's primary efficacy analysis included a total of 68 subjects with MCL who had PET-positive disease at study baseline or after bridging therapy, were treated with conforming liso-cel in intended dose range, and had a minimum of 6 months of follow up from the onset of initial response. As described under Section 8.1.1, FDA analysis took into consideration CT and/or clinical evidence of new lesions/disease progression while determining final disease response. It should be noted that per the 2014 Lugano criteria (Cheson et al. 2014), concordance between PET-CT findings and bone marrow biopsy (BMB) for the presence of bone marrow lymphoma involvement is better established for diffuse large B-cell lymphoma; for all other lymphoma subtypes, a BMB is the standard method for disease assessment in the bone marrow. For this reason, FDA considered in its assessment of ORR, that subjects on this trial deemed to have a complete response to therapy by imaging criteria must have a BMB documenting absence of disease, to be considered a complete responder if baseline BMB (or imaging) was positive for lymphoma involvement or was not performed. Table 20 below shows the discordance between baseline BMB and PET results supporting the use of a BMB to assess baseline bone marrow involvement for MCL.

Table 20: FDA Analysis – Discordance Between Bone Marrow and PET Baseline Assessments

Subject ID	Results of Baseline BM Biopsy	Results of Baseline BM PET
(b) (6)	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Positive
	Positive	Negative
	Positive	Positive
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative
	Positive	Negative

Source: FDA review of BMIRC dataset
Abbreviation: BM, bone marrow.

Data Quality and Integrity

The Applicant's Position:

Data review and quality control checks were implemented by the sponsor and consisted of site monitoring visits guided by the monitoring plan to review source documents against the eCRF and Programmed edit checks, SAS edit checks, and Team Data Review 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. The Vendor Data Quality Oversight Plan was used to ensure oversight of Data Management review performed by the Data Management Review team. In addition, a review of the database was performed by BMS Global Biometric and Data Sciences (GBDS) to enhance the quality and ensure completeness of the data. When the database was declared complete and accurate, the Database Lock Checklist was completed, which documented that all prerequisites for the database lock were achieved, and the database was locked.

The FDA's Assessment:

The FDA confirms that no data quality or integrity issues were identified.

Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Table 21: Applicant – Results of the Key Secondary Analysis in the Statistical Testing Hierarchy – PAS

	Rate (95% CI)	Null Hypothesis/ Significance Test Level	P-Value	Statistically Significant[a]
Key Secondary Objective: IRC-assessed CR rate	74.3% (62.8, 83.8)	≤ 18% 1-sided 0.025	<0.0001	Yes

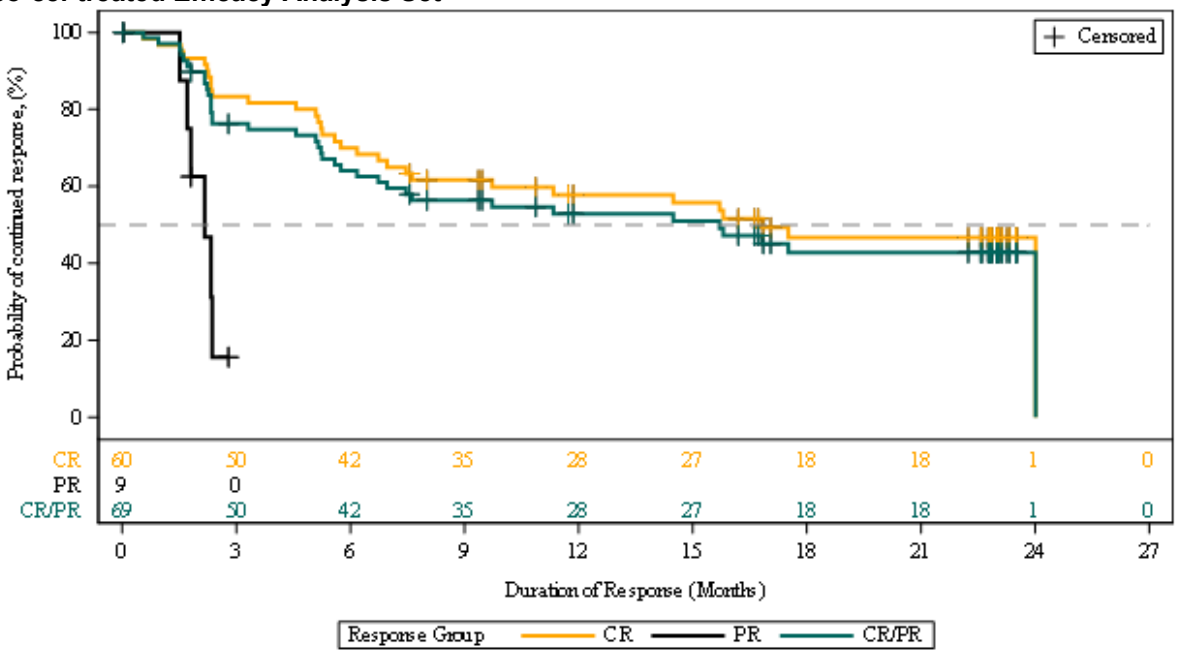
[a] 2-sided 95% exact Clopper-Pearson confidence intervals.
Source: ADSL and ADEFFSUM.

Table 22: Applicant – Summary of Key Secondary and Secondary Efficacy Endpoints in the EAS and ITT Sets

	EAS		Leukapheresed Set (ITT)	
	Per IRC N = 83	Per FDA Algorithm N = 83	Per IRC N = 104	Per FDA Algorithm N = 104
CR Rate, n (%)				
CR	60 (72.3)	57 (68.7)	64 (61.5)	60 (57.7)
95% CI [a]	(61.4, 81.6)	(57.6, 78.4)	51.5, 70.9	47.6, 67.3
DOR (Months)				
Subjects with CR or PR	69	67	73	71
Median, 95% CI[b]	15.7 (6.2-24.0)	15.7 (6.7, NR)	16.8 (7.0, 24.0)	16.8 (7.5, NR)
Min, Max	0.0+, 24.0	0.0+, 23.5+	0.0+, 24.0	0.0+, 23.5+
Median follow-up, 95% CI[c]	22.8, (16.7-23.0)	22.6 (16.9, 22.9)	22.8 (16.9, 23.0)	22.6 (16.9, 22.9)
Subjects with BOR of CR	60	57	64	60
Median, 95% CI[b]	16.8 (7.5, 24.0)	17.5 (7.5, NR)	17.5 (9.7, 24.0)	23.3 (9.7, NR)
PFS (Months)				
Median, 95% CI[b]	15.3 (6.6-24.9)	8.5 (6.0, 17.8)	11.7 (7.4, 25.0)	8.9 (4.5, 18.2)
Min, Max	0.0+, 24.9	0.0+, 24.4+	0.0+, 31.2+	0.0+, 31.2+
Median follow-up, 95% CI[c]	23.5 (17.7-23.8)	23.6 (18.0, 24.0)	24.8 (18.8, 25.2)	25.1 (19.1, 25.4)
Subjects with BOR of CR	60	57	64	60
Median, 95% CI[b]	17.8 (8.3, 24.9)	18.4 (8.5, NR)	24.8 (18.8, 25.2)	26.9 (15.2, NR)
OS (Months)				
Median, 95% CI[b]	18.2 (12.9-36.3)		19.2 (12.1, 52.4)	
Min, Max	0.4, 60.5+		0.5, 73.1+	
Median follow-up, 95% CI[c]	24.0 (23.7-24.2)		25.4 (25.1, 25.8)	
Subjects with BOR of CR				
Median, 95% CI[b]	36.3 (15.7, NR)		NA	

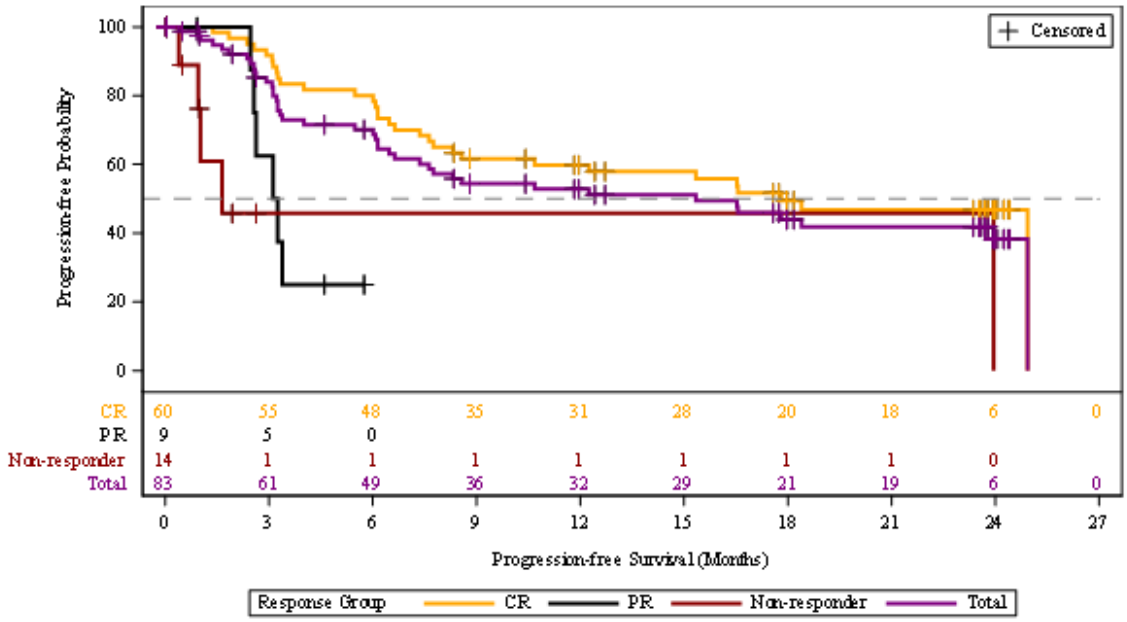
[a] **2-sided 95% exact Clopper-Pearson confidence intervals.**
[b] Kaplan-Meier (KM) method is used to obtain 2-sided 95% confidence intervals.
[c] Reverse KM method is used to obtain the median follow-up and its 95% confidence intervals.
+ Censored.
Note: FDA algorithm and ITT analyses are sensitivity analyses**.**
Source: **ADSL, ADEFFSUM and ADTTEE.**

Figure 2: Applicant – Duration of Response per IRC Assessment by Best Overall Response – Liso-cel-treated Efficacy Analysis Set



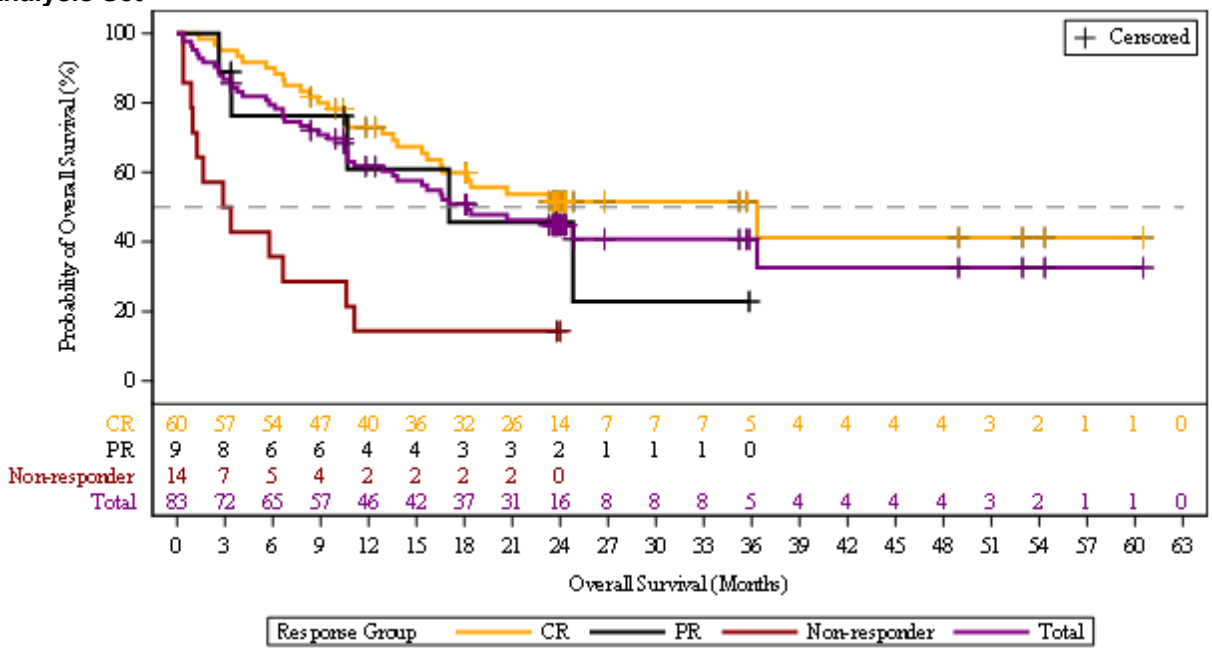
Source: ADSL, ADBASE, ADEFFSUM and ADTTEE

Figure 3: Applicant – Progression-free Survival per IRC Assessment by Best Overall Response – Liso-cel-treated Efficacy Analysis Set



Source: ADSL, ADBASE, ADEFFSUM and ADTTEE

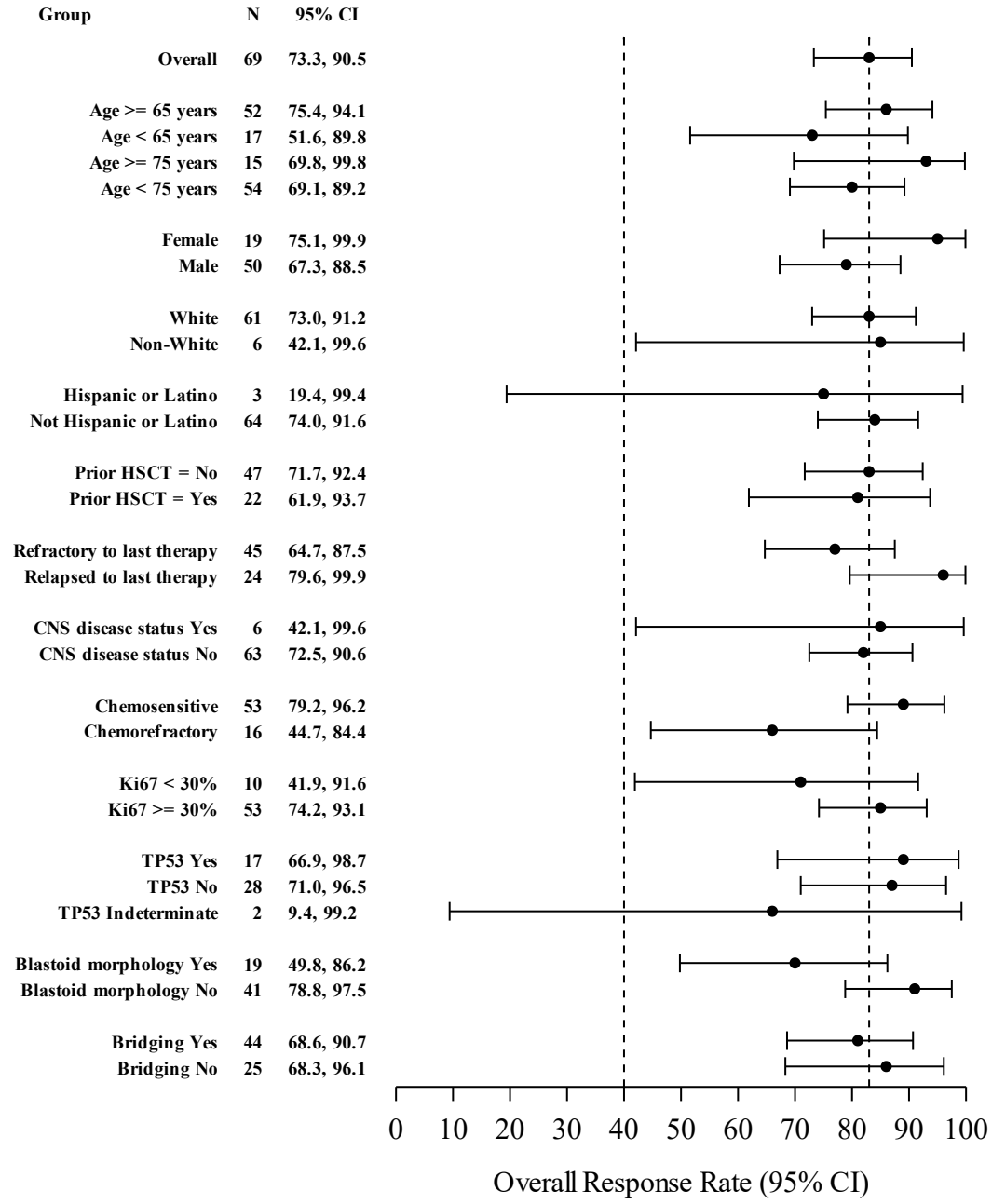
Figure 4: Applicant – Overall Survival by Best Overall Response Liso-cel-treated Efficacy Analysis Set



The OS analysis includes all available survival information with long-term follow-up data.

Source: ADSL, ADBASE, ADEFFSUM and ADTTEE

Figure 5: Applicant – Forest Plot of ORR per IRC Assessment in the EAS



ORR and 2-sided 95% exact Clopper-Pearson confidence intervals are displayed.
Source: ADSL, ADEFFSUM and ADSUBGRP

Efficacy Results to Support the USPI

Table 23: Applicant – ORR and CR (per FDA Algorithm) to Support the USPI – Leukapheresed Set (DL2S) and EAS (Dose Range 90 to 110 x 10^6 CAR+ T Cells)

	EAS 90 to 110 × 10^6 CAR+ T cells (N = 70)	Leukapheresed Set (ITT) DL2S (N = 94)
Overall Response Rate (ORR), n (%) [95% CI]	60 (85.7) 75.3, 92.9	68 (72.3) 62.2, 81.1
Complete Response (CR), n (%) [95% CI]	51 (72.9) 60.9, 82.8	57 (60.6) 50.0, 70.6
Partial Response (PR), n (%) [95% CI]	9 (12.9) 6.1, 23.0	11 (11.7) 6.0, 20.0

Note: KM method was used to obtain 2-sided exact Clopper-Pearson 95% confidence intervals.
Source: ADSL and ADEFFSUM.

Table 24: Applicant – Duration of Response (per FDA Algorithm) to support the USPI – EAS (Dose of 90 to 110 x 10^6 CAR+ T Cells)

	EAS 90 to 110 × 10^6 CAR+ T cells (N = 70)
Number responders, n (CR+PR)	60
DOR, mo.	
Median [95% CI]	14.5 (6.2-23.3)
Range	0.0+, 23.5+
DOR if best response is CR, mo.	
Median [95% CI]	16.8 (7.5-NR)
Range	0.0+, 23.5+
DOR if best response is PR, mo.	
Median [95% CI]	2.3 (1.5-13.3)
Range	1.5, 14.5
Median follow-up for DOR [95% CI], mo.	22.6 (16.7-22.8)

KM method was used to obtain 2-sided 95% confidence intervals
NR = not reached
+ = censored value
Source: ADSL, ADEFFSUM, ADSUBGRP and ADTTEE.

The Applicant's Position:

CR Rate

The key secondary endpoint (CR rate per IRC) in the prespecified statistical testing hierarchy was met, with statistically and clinically meaningful responses to treatment in the PAS (Table 21). A similar high CR rate of 72.3% was observed in the EAS per IRC (Table 22) which was consistent with the primary analysis in the PAS. In the Leukapheresed Set (ITT), IRC-assessed CR rate was numerically lower than in the PAS and in the EAS as expected. Sensitivity analyses of CR rate using the FDA algorithm yielded results consistent with those obtained by IRC assessment in PAS, EAS and ITT.

DOR, PFS, OS

Responses to liso-cel treatment were achieved rapidly (median time to response: 0.95 month) and were maintained with a median DOR of 15.7 months (95% CI: 6.2, 24.0) per IRC in the EAS with a median follow-up time of 22.8 months. Median DOR for subjects with a BOR of CR was 16.8 months (95% CI: 7.5, 24.0). Results were consistent in the ITT and per the FDA algorithm (Table 22).

At the time of the primary analysis (data cut off date of 19-Jan-2023), 10/88 (11.4%) of subjects in the Liso-cel-treated Analysis Set were ongoing in the study, with 9 of the 67 responders per FDA algorithm in the EAS remaining on study in an ongoing response. All 67 responders per FDA algorithm in the EAS had ≥ 6 months follow-up, 94.0% had ≥ 12 months and 88.1% of responders had ≥ 18 months follow up for DOR from first objective response (ADSL, ADEFFSUM and ADTTEE).

In the EAS, liso-cel was able to induce a clinically meaningful median PFS of 15.3 months (95%: CI: 6.6, 24.9) per IRC and a median OS of 18.2 months (95% CI: 12.9, 36.3), with a median follow-up time of 23.5 and 24.0 months, respectively. Greater PFS per IRC and OS benefit was observed in those achieving CR with a median PFS of 17.8 months (95% CI: 8.3, 23.9) and median OS of 36.3 months (95% CI: 15.7, NR) (Table 22, Figure 3, and Figure 4).

Investigator-assessed CR rate (72.3% [95% CI: 61.4, 81.6]) , DOR (15.0 months [95% CI: 6.5, NR]), and PFS (8.3 months [95% CI: 5.7, 16.8]) in the EAS was consistent with IRC assessment, suggesting a low impact of bias, disease heterogeneity, and evaluation variability among assessors (ADSL, ADEFFSUM and ADTTEE).

Similar efficacy was observed in subjects with poor prognostic features, including TP53 mutations, blastoid morphology, Ki67 ≥ 30%, and secondary CNS disease for ORR (Figure 5), CRR per IRC and DOR per IRC and ORR and CRR per FDA algorithm.

To evaluate the effect of number of prior LoT on liso-cel efficacy outcomes, a post-hoc analysis was performed on ORR, CRR, and DOR per FDA algorithm in the EAS DL2S population for groups of subjects receiving ≤ 2, > 2, 3-4, and > 5 prior LoT. Acknowledging the limitation of the analysis due to the small sample size of the single groups, in the EAS DL2S subgroup analysis, liso-cel showed the following (ADSL, ADBASE, ADEFFSUM, ADSUBGRP and ADTTEE):

- Robust efficacy outcomes (ORR and CRR) comparable to the overall EAS DL2S group were observed regardless of the number of prior LoT, ranging from 77.8% to 88.5% for ORR and 63.0% to 80.8% for CRR in the EAS DL2S LoT subgroups.
- A trend of numerically higher median DOR among less heavily pretreated subjects was observed: not reached in subjects with ≤ 2 LoT (n = 27) vs 9.7 months in more heavily pretreated subjects (> 2 LoT [n = 50]) in all responders, as well as in subjects with a BOR of CR (not reached for ≤ 2 LoT and 11.3 mo. For > 2 LoT). A similar trend of longer durability of response in less heavily pretreated subjects was observed when further subdividing the > 2 LoT category

to compare subjects who received 3 to 4 versus ≥ 5 prior LoT: median DOR was 17.5 months vs 6.2 months, respectively.

- The 2 subjects who had only 1 prior LoT achieved CR and long DORs (16.8 and 23.3 months).

Results in the Proposed Dose Range for the USPI

In the EAS (DL2S), 70 of 77 (90.9%) subjects were administered liso-cel in the proposed dose range of 90 to 110 × 106 CAR+ T cells (Table 23). In the EAS population receiving 90 to 110 × 10^6 CAR+ T cells, liso-cel demonstrated a high ORR (85.7%) and CRR (72.9%), with a median DOR of 14.5 months per FDA algorithm at a median follow up time of 22.6 months; these results were comparable to the overall EAS and EAS (DL2S) (Section 6). Similarly, robust efficacy outcomes (ORR and CRR) were observed regardless of the number of prior LoT (≤ 2 vs > 2), ranging from 76.9% to 90.9% for ORR and 61.5% to 79.5% for CRR (ADSL, ADBASE, ADEFFSUM, ADSUBGRP and ADTTEE). A numerically higher median DOR was observed among less heavily pretreated subjects (not reached in subjects with ≤ 2 LoT [n = 26] vs 7.5 months in more heavily pretreated subjects > 2 LoT [n = 44]) in all responders as well as in subjects with a BOR of CR (not reached for ≤ 2 LoT and 9.7 mo. For > 2 LoT).

Additional Follow-up for Time-to-event Efficacy Outcomes

In addition, to further support the robustness and durability of liso-cel efficacy outcomes, data with an additional 4 months of follow-up based on a later data cutoff date of 23-May-2023 were analyzed for DOR follow-up times and the primary and secondary efficacy endpoints. At this cutoff date, for all responders in the EAS per FDA algorithm, all subjects had ≥ 9 months follow-up for DOR from first objective response, and 97.0% and 94.0% of subjects had ≥ 12 months and ≥ 18 months of follow-up time for DOR, respectively (ADSL, ADEFFSUM and ADTTEE). The study followed subjects through 24 months after liso-cel infusion, allowing for up to 23 months of follow up from first objective response. Among the subjects with an ongoing response/remain at risk, the majority have completed the study at the 23-May-2023 cutoff date. Of the 67 responders, 4 responders with an ongoing response remained on study; all 4 subjects will have their EOS visit by the end of Q1-2024. The study is planned to be completed in May 2024 when the LSLV is anticipated.

The FDA's Assessment:

The FDA primary efficacy analysis was limited to subjects with R/R MCL who received at least two prior lines of therapy including a BTKi, received the intended commercial dose, and had a minimum of 6 months of follow up for duration of response. As two subjects in the Applicant's proposed USPI population did not receive at least 2 prior lines of therapy including a BTKI, an updated efficacy analysis, based on 68 subjects was performed as summarized below in Table 25. Response assessments were adjudicated by the FDA clinical team using both the FDA adjudicated IRC analysis and the IRC Charter (Refer to Section 8.1.1 Study 017001 for further details). The table also summarizes the efficacy data for the intention to treat population (i.e., all leukapheresed

population).

Table 25: FDA Analysis – Response Rate in Relapsed or Refractory MCL (Study 017001-MCL Cohort)

Response Rate	Primary Efficacy Population, adjudicated IRC FDA algorithm (N=68)	Primary Efficacy Population, per IRC Charter (N=68)	All Leukapheresed Patients (N=89)
Overall Response Rate*, n (%)	58 (85.3)	60 (88.2)	65 (73.0)
[95% CI]	74.6, 92.7	[78.1, 94.8]	62.6, 81.9
Complete Response, n (%)	46 (67.6)	52 (76.5)	51 (57.3)
[95% CI]	55.2, 78.5	[64.6, 85.9]	46.4, 67.7
Partial Response, n (%)	12 (17.6)	8 (11.8)	14 (15.7)
[95% CI]	9.5, 28.8	[5.2, 21.9	8.9, 25.0

Source: FDA's primary review of INTEFF, ADLS, ADRS, ADTTEIRC, ADTR/TU, ADBM datasets, clinical study report and FDA statistical reviewer's memo
*Response per IRC charter was assessed as per modified Lugano criteria (Refer to Section 8.1.1 Sensitivity Analyses and FDA Assessment)
Abbreviations: CI. Confidence interval; IRC, independent review committee; MCL, mantle cell lymphoma.

FDA's analysis includes a change in best overall response for a total of 16 subjects as detailed in Appendix 17.2. Although efficacy analyses using both methods show similar ORR, the CRRs are slightly lower per the FDA analysis. Since response assessment using FDA's analysis is based on a standard Lugano 2014 classification, the clinical review team recommends including ORR per the IRC FDA analysis in the label.

Subjects were downgraded based on the FDA analysis due to the requirement for a BMB to confirm CR, progressive disease on CT scan, and/or clinical PD.

There were three subjects with discordant PET interpretations between the IRC and the IRC FDA algorithm reads, as noted below. The FDA used the IRC assessments for the following subjects:

- Subject (b) (6) (response assessment of PR, per IRC assessment): At the Day 29 visit, per IRC, the overall time point response was PR. At the Day 29 visit, per IRC-FDA analysis, the overall time point response was CR. The Day 29 CT scan showed a response of PR. The review team assesses that the response remain a PR, based on the IRC.
- Subject (b) (6) (response assessment of PR, per IRC assessment): At the Day 29 visit, per IRC, the overall time point response was PR. At the Day 29 visit, per IRC-FDA analysis, the overall time point response was CR. Different response assessments are due to differences in PET assessments by different radiologists for IRC and for FDA analysis. The review team assesses that the response remains a PR based on the IRC.
- Subject (b) (6) (response assessment of PR, per IRC assessment): At the Day 29 visit, per IRC, the overall time point response was PR. At the Day 29 visit,

per IRC-FDA analysis, the overall time point response was CR. An adjudication was triggered based on a difference in PET Best Response between the two independent radiologists. Radiologist # 2 assessed an area of residual PET avidity within the spleen leading to an assessment of PR. The adjudicator indicated difficulty in determining whether the splenic uptake indicated a true site of disease or a calcification, which explains the two different assessments for the same time point response. The review team assesses that the response remain a PR based on the IRC.

Post-treatment follow-up: Subjects were followed for 24 months on study for safety, disease status, additional anticancer therapies, and survival following treatment prior to the long-term follow-up (LTFU) period. The majority of subjects included in the USPI efficacy population did not consent to the LTFU study, so longer safety follow-up is not available for the majority of subjects.

Non-conforming product

Table 26: FDA – Outcomes for the Subjects Who Received Non-Conforming Products (n=4)

Subject ID	Dose	BOR per FDA Algorithm
017001 (b) (6)	51.886765	CR
017001	99.408088	SD
017001	85.632090	PR
017001	99.607750	SD

Source: FDA Review of ADEX and ADRS dataset from Study 017001 MCL Cohort
Abbreviations: BOR, best overall response; CR, complete response; FDA, US Food and Drug Administration; PR, partial response; SD, stable disease.

Dose/Dose Response

The Applicant's Position:
Two dose levels were evaluated in the Study 017001 MCL Cohort. Based on cumulative data, the SC recommended DL2S regimen for the MCL Cohort (see Rationale for Dosing Regimen Selection in Section 6).

The FDA's Assessment:

The FDA notes that responses were observed at lower doses but agrees with the Applicant's assessment. Refer to the clinical pharmacology memo for details.

Durability of Response

The Applicant's Position:
See DOR and PFS results under Secondary Endpoints above.

The FDA's Assessment

With a median duration of follow up for response of 22.2 months, responses were durable, as detailed in Table 27 below.

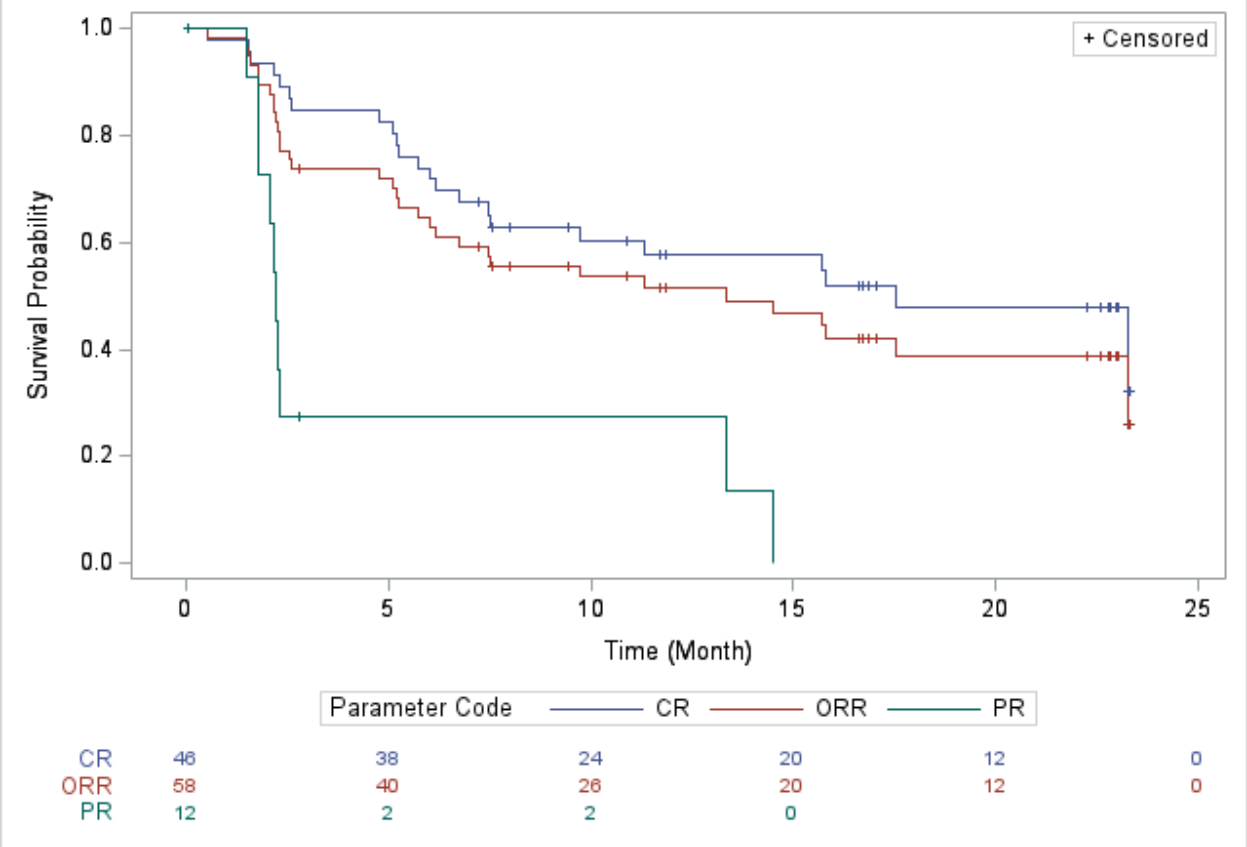
Table 27: Duration of Response[a] in FDA Efficacy Population per IRC FDA Algorithm, FDA Adjudicated

DOR Parameter	Primary Efficacy Population (N=68)
ORR n (%)	58 (85.3%)
Median DOR[b] (95% CI)[c]	13.3 (6.0, 23.3)
DOR[b] estimates	-
Rate at 12-months, % (95% CI)[d]	51.4 [37.5, 63.7]
Rate at 18-months, % (95% CI)[d]	38.8 [25.0, 52.4]
DOR events or censoring status, n (%)	-
Censored	25 (43%)
Event	33 (57%)
Progressive Disease	23 (69)
Death	10 (30.3)
Censored	25 (43%)
Alive without PD before data cutoff	9 (36%)
Completed study without PD or death	13 (52%)
Discontinued study without PD or death	1 (0

Source: FDA Statistical Analysis, FDA Analysis of ADSL, INTEFF.
[a] Median follow-up for DOR is 22.2 months (95% CI: 16.7 to 22.8)
[b] Per the 2014 Lugano Classification (including bone marrow biopsy assessments), as assessed by IRC.
[C] Kaplan-Meier method was used to obtain 2-sided 95% CIs.
[D] Kaplan-Meier estimate of probability of continued response at the specified month.

The KM plot of DOR per IRC FDA analysis for the FDA Primary Analysis Set (PAS) for efficacy (N=68) is shown in Figure 6 below. As shown below, the DOR is mainly driven by patients whose BOR was CRR.

Figure 6: Kaplan-Meier Plot of DOR by IRC FDA Algorithm for the Efficacy Analysis Population (n=68), FDA Adjudicated



Source: FDA Statistical Analysis

Persistence of Effect

The Applicant's Position:
See DOR and PFS results under Secondary Endpoints above.

The FDA's Assessment:

The median DOR of 13.3. months was considered durable for this R/R population. See above for details. This trial is a single-arm study with no comparator group; hence, time-to-event endpoint (such as PFS, OS) data are not interpretable. Therefore, the PFS and OS data have limited value in benefit risk assessment and should be interpreted with caution. See statistical reviewer memo for further information on these endpoints.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

- **EORTC QLQ-C30**: Liso-cel demonstrated improvements in evaluations of group-level mean change from baseline on most EORTC QLQ-C30 domains in patients. Including fatigue, global health status/QoL, and physical functioning. Pain was stable

through the first year (ADSL and ADQLQ).

- **EQ-5D-5L Index Score**: The EQ-5D-5L Index Score group-level mean remained consistent over the course of the study (from baseline to Month 24 post dose) for all subjects (total[DL1S+DL2S]) in the PRO/QoL (EQ-5D) Evaluable Set (ADSL and ADEQ5D).
- **EQ-5D-5L VAS:** For all subjects (total [DL1S+DL2S]) in the PRO/QoL EQ-5D-5L Evaluable Set, HRQoL measured by the EQ-5D-5L VAS improved from baseline to Month 2 (mean change (SD) in VAS = 11.0 (22.7), and the improvement remained consistent until Month 18 (ADSL and ADEQ5D). The mean change in the VAS decreased at Month 24 to a non clinically meaningful (mean change (SD)=3.5 (30.8) improvement from baseline.
- **HRU:** Hospitalization may have been required after treatment with liso-cel to manage any treatment associated toxicities. Administration of liso-cel as inpatient or outpatient setting was determined at the PI's discretion.
  In the 75 subjects who received liso-cel and were monitored as inpatients, the most common reason for hospitalization during liso-cel infusion was prophylaxis for CAR+ T-cell administration (66 [88.0%] subjects) (ADSL, ADHO and ADHOSUM). For these 75 subjects, the median duration of initial hospitalization from liso-cel administration was 11 days (range: 2 to 31), and 5 subjects were admitted to the ICU (median duration = 5 days [range: 2 to 38]).
  In the 13 subjects who received liso-cel and were monitored as outpatients, 12 were admitted after infusion due to Aes (ADSL, ADHO and ADHOSUM). For these 12 subjects, the median duration of initial hospitalization after liso-cel administration was 6.5 days (range: 2 to 43). 1 subject was admitted to the ICU for 6 days.

The Applicant's Position:
Although compliance rate for all HRQoL questionnaires largely decreased over time (typically due to administrative and logistical delays around the implementation of the PROs in the study), liso-cel treatment consistently demonstrated clinically meaningful improvements over time in evaluations of group level mean change from baseline on many EORTC QLQ-C30 domains and the EQ-5D-5L VAS. Liso-cel administration in the outpatient setting was associated with a shorter duration of hospitalization. The overall rate of ICU admission was low.

The FDA's Assessment:

The Applicant submitted patient reported outcomes (PROs) collected using different PRO instruments (EORTC QLQ-C30, EQ-5D-5L index score, EQ-5D-5L visual analog scale [VAS], and hospital resource utilization [HRU]). However, because the study is a single-arm study, the PRO data are descriptive and are not considered for regulatory decision making.

Additional Analyses Conducted on the Individual Trial

Data:

Post-hoc Sensitivity Analysis on COVID-19 Impact
The majority of the subjects (75%) were treated during the COVID-19 pandemic and most of the on-study follow up (median of 16.10 months) occurred during the pandemic which was still ongoing at the time of the primary analysis (data cutoff date 19-Jan-2023). 7 subjects in the PAS and in the EAS died due to COVID-19 (1 in the treatment emergent period and 6 in the post-treatment emergent period). 6 subjects with a CR died in ongoing response within the first year post-liso-cel (Day 72 to 325), and the last subject died after experiencing PD. To evaluate the effect of treatment in the absence of the pandemic37,38,39, a post-hoc sensitivity analysis on the impact of COVID-19-related deaths was conducted, which summarized DOR, PFS, and OS by censoring the subjects who died because of COVID-19 in ongoing CR as discontinued from the study for DOR and PFS and alive for OS, and by censoring the subject who died of COVID-19 after experiencing PD as alive for OS.

Compared with the EAS:
- The median DOR in the COVID-19 sensitivity analysis was numerically longer: 17.5 months (95% CI: 7.6, 24.0) vs 15.7 months (95% CI: 6.2, 24.0).
- The median PFS in the COVID-19 sensitivity analysis was numerically longer, 17.8 months (95% CI: 7.6, 24.9) vs 15.3 months (95% CI: 6.6, 24.9).
- The median OS in the COVID-19 sensitivity analysis was numerically longer, 24.8 months (95% CI: 15.7, NR) vs 18.2 months (95% CI: 12.9, 36.3).

The Applicant's Position:
These data show that efficacy outcomes were potentially impacted by the COVID-19 pandemic.

The FDA's Assessment:

Post-hoc sensitivity analysis was not part of this review and cannot be confirmed.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

This section is not applicable.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:

This section is not applicable.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

In the PAS, the primary and key secondary objectives for the Study 017001 MCL Cohort were met:

- Primary endpoint: ORR per IRC of 86.5% (95% CI 76.5 – 93.3; p value < 0.0001)
- Key secondary endpoint: CRR per IRC of 74.3% (95% CI 62.8 – 83.8; p value < 0.0001)

In the EAS:

- Liso-cel provided robust, rapid, and durable responses with clinically meaningful PFS and OS in a R/R MCL population with advanced age, heavily pretreated, aggressive disease, and moderate renal and cardiac comorbidities.
- Greater DOR, PFS, and OS benefit was observed in those achieving CR.
- Efficacy outcomes were consistent across population analysis sets and within sensitivity analyses, including investigator assessment and FDA algorithm.
- Similar efficacy was observed in subjects with poor prognostic features, including TP53 mutation, blastoid morphology, and Ki-67 expression ≥ 30%, and secondary CNS involvement.

Efficacy analysis results for liso-cel in PAS and EAS were robust despite the effect of the COVID-19-related deaths in ongoing complete response.

Patient experience data based on PROs showed that overall patients experienced meaningful and sustained improvements with liso-cel treatment in most domains of HRQoL.

At the proposed dose range of 90 to 110 × 106 CAR+ T cells in the EAS:

- Liso-cel resulted in rapid, clinically meaningful ORR (85.7%) and CRR (72.9%), and median DOR of 14.5 months per FDA algorithm at a median follow up time of 22.6 months.
- Robust ORR and CRR was confirmed between subjects receiving ≤ 2 prior LoT vs subjects receiving > 2 LoT. Additionally, there was a trend in improved mDOR in the less pretreated population.

Taken together, these results indicate that liso-cel confers clinically meaningful benefit to patients with R/R MCL after BTKi, as demonstrated by the high rate of and deep durable objective and complete responses observed at the 90 to 110 × 106 cells dose level. The improved mDOR observed in subjects with ≤ 2 prior LoT (compared with> 2 prior LoT) supports the benefit of liso-cel in a less pretreated patient population.

The FDA's Assessment:

FDA disagrees with the Applicant's assessment that based on the data from study 017001, liso-cel confers clinically meaningful benefit to patients with R/R MCL after BTKi, as this population is broad and does not reflect the majority of the study population who had received at least at least 2 prior lines of therapy including a BTKi. Given that only 2 subjects received less than 2 prior lines of systemic therapy, conclusions cannot be drawn regarding the benefit of liso-cel in this less heavily pretreated patient population.

FDA's primary efficacy analysis is limited to subjects who received 90 to 110 × 10^6 CAR+ T cells and excludes subjects who received less than 2 prior lines of therapy (n=2). The median number of prior systemic therapies was 3 (range 2-11) in the FDA PAS and represents a heavily pretreated population.

FDA's efficacy analysis considered the IRC-assessed responses per Lugano 2014 and additionally, included assessments reflecting response not completely addressed in the Applicant's IRC assessment to include evidence of clinical progression without radiographic progression and adequate assessment of bone marrow involvement to determine complete response. In addition, responses when discordance between investigator and IRC assessments were adjudicated by FDA.

Durability of response is an important consideration in the overall assessment of efficacy. All responders had at least 6 months of follow up from first response to allow for an adequate assessment of durability of response.

Mantle cell lymphoma is an aggressive B-cell malignancy. Outcomes are particularly poor for patients who fail standard therapies including a BTKi with median OS less than 8.4 months (Hess et al. 2022). Based on the totality of the efficacy data, the durable ORR of 85%, and CR rate of 68% in adult patients with R/R mantle cell lymphoma who have received at least 2 prior therapies including a BTKi, represents clinically meaningful efficacy.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:
Safety was a co-primary endpoint of Study 017001 and included type, frequency and severity of Aes and laboratory abnormalities as well as assessment of the probability of dose-limited toxicity.
The Liso-cel-treated Analysis Set (N = 88), defined as all subjects who received at least 1 dose of liso-cel, was used to characterize the safety profile of liso-cel in subjects with R/R MCL. Safety analyses are focused on TEAEs, defined as any AE that started any time from initiation of liso-cel administration through and including 90 days following the final cycle of liso-cel administration.
Safety data from the primary analysis (data cut off date of 19-Jan-2023) for the 88 subjects in the Liso-cel-treated Analysis Set are presented in Sections 8.2.4 to 8.2.9.
To allow a comparison of the safety profile of liso-cel monotherapy in MCL versus the known safety profile in LBCL, safety data for the MCL subjects in the Liso-cel treated Analysis set are also presented side-by-side with the pooled safety data of the 418 LBCL subjects included in the current USPI (3L+ LBCL [017001 DLBCL Cohort] plus 2L LBCL [BCM-003 and 017006]) (Section 8.2.11).

The FDA's Assessment:

FDA's safety review was focused on two cohorts of patients treated with liso-cel:

Primary MCL Safety Population: includes 88 Liso-cel treated (conforming product) patients with R/R MCL who received DL1S or DL2S (i.e., 50 to 110 $X10^6$ cells). An additional safety review, restricted to subjects who received DL2S (i.e., $100X10^6$ cells), was also performed; the safety profile in this group was similar as compared to the broader population which included both DL1 (N=6) and DL2 (N=82). The rationale to evaluate safety in the entire treated population of DL1S and DL2S was to capture rare events and provide a more comprehensive analysis in patients with MCL.

The safety population also included two subjects who did not receive a prior BTKi.

- Integrated Safety Population: includes 966 Liso-cel treated patients:
  - 582 LBCL patients, 118 R/R CLL/SLL, 130 FL, 88 R/R MCL, 48 MZL Pooled Safety Population

The integrated safety dataset is considered supportive only.

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

- ADAM datasets
- Case report forms and safety narratives
- Applicant submissions in response to the review team's information requests
- Prior regulatory history
- Proposed labeling for liso-cel
- Protocol and statistical analysis plan
- Clinical study report of safety for Study 017001

AEs were coded using the Medical Dictionary for Regulatory Activities version 25.1, and AE severity was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. CRS severity was graded according to a modification of the 2014 Lee grading system (Lee et al. 2014). Some AEs are presented throughout this review as FDA-grouped preferred terms as defined by the review team (See Appendix 19.1). AEs that involve more than one body system were consolidated and reported under the most commonly involved or most appropriate body system. Unless noted, all presented analyses use the FDA-grouped preferred terms. All analyses were performed using JMP16 (SAS Institute, Inc.).

SAEs were defined as any AEs that met at least one of the following criteria: fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, disability/incapacity, congenital anomaly/birth defect, or medically important.

Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring or

worsening within 90 days after the infusion of liso-cel or the start of new antineoplastic therapy, whichever came first. AEs were analyzed with a focus on TEAEs in Section 8.2.

Furthermore, the review process also involved the review of a 90-day safety report and adverse event dataset submitted by the Applicant on February 29, 2024 with the data cutoff date of May 23, 2023 and provides an additional 4 months of follow-up versus the previous data cutoff used for the Study 017001 Addendum 02 CSR1 (19-Jan-2023). No additional subjects were enrolled and treated since the previous data cutoff of 19-Jan-2023. No new safety signals were identified.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Lymphodepleting Chemotherapy

In the Liso-cel-treated Analysis Set (ADSL and ADEX),

- Median time from end of LDC to liso-cel infusion was 4 days, consistent with the protocol-recommended time of 3 to 7 days.
- Most subjects (71.6%) received the full specified dose of fludarabine and cyclophosphamide.
- Dose reductions were most frequently reported for fludarabine as required per protocol and per product package information based on reduced creatinine clearance.

Manufacturing

In the Leukapheresed Set (ADSL and ADMFG),

- 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 24.5 days.
- The median time from leukapheresis to liso-cel infusion day was 39.0 days.
- The manufacturing failure rate (defined as 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) was low (5.8%). Of the 6 subjects with manufacturing failure, 4 were infused with nonconforming product.

Liso-cel Treatment

Table 28: Applicant – Liso-cel Exposure – Liso-cel-treated Analysis Set

	Median (Min, Max) Dose (x 10^6 cells)		
	DL2S N=82	**DL1S N=6**	**Total N=88**
CD8	49.8 (16[a], 56)	24.9 (22, 28)	49.7 (16[a], 56)
CD4	49.5 (35, 52)	25.0 (24, 26)	49.4 (24, 52)

	Median (Min, Max) Dose (x 10^6 cells)		
	DL2S N=82	**DL1S N=6**	**Total N=88**
Total Dose	99.6 (62, 103)	49.9 (46, 54)	99.5 (46, 103)
Subjects received additional cycles, n (%)	0	1 (16.7)	1 (1.1)
Subjects received retreatment, n (%)	2 (2.4)	0	2 (2.3)

[a] After the DBL, a data entry error was found for 1 subject for the infused volume of the CD8 component. This subject was administered the assigned DL2S CD8 component dose of 50× 10^6 CAR T cells, and actually received a total dose of ≥ 90× 10^6 CAR+ viable T cells.
Source: ADSL and ADEX.

The Applicant's Position:
The overall exposure to liso-cel in 88 subjects in the Liso-cel treated Analysis Set of the MCL Cohort of Study 017001 is considered adequate to support characterization of its safety profile in subjects with R/R MCL.

The FDA's Assessment:

The FDA agrees with the Applicant's statement, however longer-term safety beyond 24 months has not yet been established in this patient population. Forty-five of eighty-eight treated subjects died prior to longer term follow-up; the majority of deaths were due to disease progression.

Relevant characteristics of the safety population:
The Applicant's Position:
The demographics and baseline characteristics (Table 12) of the Liso-cel-treated Analysis Set were representative of an older R/R MCL population with relevant comorbidities.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of demographics of the safety population summarized in Table 12.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
The Applicant's Position:
Refer to Table 14 (other baseline disease characteristics) and Table 15 (prior treatments).

The FDA's Assessment:

The FDA agrees with the Applicant's summary of baseline characteristics for the safety population summarized in Table 14.

Adequacy of the safety database:

The Applicant's Position:

The number of patients in the Liso-cel-treated Analysis Set and duration of follow-up are considered adequate to provide a reasonable estimate of adverse reactions that may be associated with liso-cel use in the R/R MCL population.

The FDA's Assessment:

The FDA agrees with the Applicant's position; however, because the majority of subjects died and/or did not consent to follow-up beyond 24 months, longer-term safety has not been established.

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 all treated subjects, including AESIs, fatal Aes and SAEs, 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's statement.

Categorization of Adverse Event

The Applicant's Position:

All Aes were coded using MedDRA Version 25.1. The severity of each AE was graded by the Investigator using NCI CTCAE version 4.03 or higher, unless otherwise specified in the 017001 Protocol. If 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 intensity of the AE. CRS toxicity was graded according to the Lee criteria.[40] The individual symptoms of CRS were graded according to the NCI CTCAE v4.03 criteria.

Aes were analyzed with a focus on TEAEs, defined as any AE that started any time from initiation of liso-cel administration through and including 90 days following the final cycle of liso-cel administration. Any AE occurring after the initiation of another anticancer treatment or liso-cel retreatment 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.

An AESI is an AE of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the Investigator to the Sponsor. AESIs for liso-cel included CRS, iiNT, IRR, MAS, TLS, Grade ≥ 3 infections, prolonged cytopenia (defined as any Grade ≥ 3 laboratory result of decreased hemoglobin, ANC, or platelets at the Day 29 Visit), hypogammaglobulinemia, SPM, and

autoimmune disorders. Manifestations of iiNT were to be reported as individual Aes and grouped into 8 categories of NESI (encephalopathy, aphasia, tremor, delirium, dizziness, headache, anxiety, and insomnia).
The focus of laboratory data summarization (includeing hematology, serum chemistry) was on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by at least 1 grade within 90 days after the final cycle of investigational product.
Hematological and serum biochemistry data were graded according to CTCAE v4.03, when applicable. Grade 0 includes all non-missing values that do not meet the criteria for an abnormality of at least Grade 1. Grade 5 was not used.

The FDA's Assessment:

The FDA agrees with the Applicant's summary.

The Applicant summary of adverse events of special interest (AESIs) (Table 35) is limited to treatment-emergent events, defined as events occurring within 90 days of liso-cel infusion. The FDA review also included review of SPM AESIs and deaths beyond Day 90 which included review of safety narratives provided for individual subjects who experienced at least one qualifying event while participating in Study JCAR017-017001, which was approximately 24 months after the dose of liso-cel (patients were offered a subsequent LTFU study). A summary of those events captured within the 24-month study period is provided in respective sections.

Routine Clinical Tests

The Applicant's Position:
Clinical laboratory evaluations included hematology, coagulation, clinical chemistry, immunoglobulins, coagulation, inflammatory markers, HLA typing, persistence vector sequencing (PVS) monitoring, and replication-competent lentivirus (RCL) testing.

The FDA's Assessment:

FDA agrees with Applicant's position.

8.2.4. Safety Results

Table 29: Applicant – Overall Summary of Safety – MCL Cohort

Safety Parameter	Number (%) of Subjects
Leukapheresed Set	**N = 104**
Overall number of deaths between leukapheresis and LDC	8 (7.7)
Overall number of deaths between LDC and liso-cel infusion	1 (1.0)
Overall number of deaths after liso-cel infusion	48 (46.2)
Primary cause of death	
Disease progression	31 (29.8)
AE	9 (8.7)
Unknown	1 (1.0)

Safety Parameter	Number (%) of Subjects
Other	7 (6.7)
Liso-cel-treated Analysis Set	**N = 88**
Subjects with any TEAE	88 (100)
Subjects with any Grade ≥3 TEAE	76 (86.4)
Subjects with any Grade 5 TEAE	4 (4.5)
Subjects with any treatment emergent SAE	47 (53.4)
Subjects with any liso-cel-related TEAE[b]	77 (87.5)
Subjects with any liso-cel-related Grade ≥3 TEAE	43 (48.9)
Subjects with any liso-cel-related Grade 5 TEAE	3 (3.4)
Subjects with any liso-cel-related treatment emergent SAE	34 (38.6)
Subjects with any LDC-related TEAE	74 (84.1)
Subjects with any treatment-emergent AESI	
CRS	54 (61.4)
iiNT	27 (30.7)
Prolonged Cytopenia	35 (39.8)
Grade ≥ 3 Infection	13 (14.8)
MAS	0
Hypogammaglobulinemia	6 (6.8)
IRR	2 (2.3)
SPM	3 (3.4)
TLS	2 (2.3)
Autoimmune Disorders	0

iiNT was defined as events from the nervous system disorders or psychiatric disorders (ND/PD) system organ classes reported in subjects who received liso-cel and for whom the investigator identified the event(s) as a CAR+ T-cell-related neurological toxicity by selecting the CNS AE checkbox and related to liso-cel on the AE eCRF.
Infection includes Grade ≥ 3 TEAEs from Infections and Infestations SOC, by HLGT.
MAS was reported as the PT haemophagocytic lymphohistiocytosis.
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.
SPM includes post-liso-cel Aes in Malignancies SMQ and Pre-malignant conditions SMQ and subsequent medical review by and adjudication panel. The adjudication process consists of reviewing of preferred terms detected during the SMQ search and selecting Aes clinically appropriate for inclusion as malignancies.
Autoimmune disorders include post-liso-cel Aes with HLGT 'Autoimmune disorders' plus the additional PTs: Temporal arteritis, Granulomatosis with polyangiitis, Behcet's syndrome and Basedow's disease, Vasculitis and erythema nodosum.
Sources: ADSL, ADAE and ADLABSUM.

Deaths

The Applicant's Position:

In the ITT set, most deaths occurred in the posttreatment period (> 90 days postinfusion) and were due to disease progression (Table 29). In the Liso-cel-treated Analysis Set, Grade ≥3 TEAE were reported in 86.4% of the subjects. Overall, 4 (4.5%) subjects experienced a Grade 5 TEAE, 3 of which were assessed as related to liso-cel: (1) COVID-19 pneumonia – related to liso-cel/LDC, (2) cryptococcal meningoencephalitis – related to liso-cel/LDC, (3) tumor lysis syndrome – related to liso-cel; the remaining Grade 5 TEAE was a cardiorespiratory arrest – not related to liso-cel/LDC/study procedure (ADSL and ADAE).

The FDA's Assessment:

Deaths:

There were 9 Grade 5 AEs during the course of the 24-month study, of which 4 were considered treatment-emergent (i.e., occurred within 90 days of liso-cel treatment) and 4 considered by the Applicant as related to liso-cel. See below Table 30 for details.

Table 30: FDA – Grade 5 Events Due to AEs

Subject ID	G5 Event High Level Term (MedDRA Derived)	Study Day Start of Adverse Event	Relationship to LDC or liso-cel per Applicant	FDA Assessment
(b) (6)	Cryptococcal meningoencephalitis#	42	Related	Related
	COVID-19	236	Not Related	Possibly Related*
	Squamous cell carcinoma of skin	560	Not Related	Not Related
	Cardio-respiratory arrest#	59	Not Related	Not related
	COVID-19	253	Related	Related
	COVID-19 pneumonia#	72	Related	Related
	Tumor lysis syndrome#	12	Related	Possibly Related, subject died in the setting of CRS and PD**
	COVID-19 pneumonia	187	Not Related	Not Related
	Diffuse alveolar damage	38	Not Related	Not Related; subject received subsequent therapy prior to event

Source: ADAE, Applicant provided safety narratives, and FDA Information Requests.
Abbreviations: AE, adverse event; LDC, lymphodepleting chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities.# Treatment-emergent

* (b) (6) On Day 49, the subject was hospitalized due to Grade 3 COVID-19. On Day 236, the subject died due to COVID-19. No autopsy was performed. IgG levels on Day 92 and Day 199 were 113 and 142, respectively (normal range 650-1600 mg/dL).

** Subject (b) (6) : This subject experienced events of shock (Grade 4; related to liso-cel; not related to LDC/study procedure; Day 10); CRS (Grade 4; related to liso-cel; not related to LDC/study procedure; Day 11); and tumor lysis syndrome (Grade 5; related to liso-cel; not related to LDC/study procedure; Day 12). The Applicant considered cause of death related to tumor lysis syndrome although there were several

events ongoing at the time of death including CRS; the exact etiology may be multifactorial and CRS as a cause of death cannot be excluded.

Additional Death (during LDC; not treatment-emergent)

Subject (b) (6) died due to a retroperitoneal haemorrhage at the time of LDC. At the time of LDC, the subject had pre-existing Grade 4 thrombocytopenia and Grade 3 anemia, for which the subject had received several units of platelets and red blood cells. On the same day of LDC administration, the subject developed a Grade 4 retroperitoneal haemorrhage. The next day the subject died due to a retroperitoneal haemorrhage. The subject did not receive liso-cel.

Serious Adverse Events

Data:

Table 31: Applicant – Treatment-emergent Serious Adverse Events Reported in ≥ 2 Subjects by System Organ Class and Preferred Term - Liso-cel-treated Analysis Set

System Organ Class Preferred Term	Number (%) of Subjects N=88
Subjects with any Serious TEAE	**47 (53.4)**
Immune system disorders	21 (23.9)
Cytokine release syndrome	21 (23.9)
Infections and infestations	9 (10.2)
Upper respiratory tract infection	2 (2.3)
Nervous system disorders	8 (9.1)
Encephalopathy	2 (2.3)
Psychiatric disorders	7 (8.0)
Confusional state	5 (5.7)
Mental status changes	2 (2.3)
General disorders and administration site conditions	4 (4.5)
Pyrexia	3 (3.4)
Metabolism and nutrition disorders	4 (4.5)
Decreased appetite	2 (2.3)
Respiratory, thoracic and mediastinal disorders	2 (2.3)
Pleural effusion	2 (2.3)

Source: ADSL and ADAE.

Table 32: Applicant – Liso-cel-related Treatment-emergent Serious Adverse Events Reported in ≥ 2 Subjects by System Organ Class and Preferred Term - Liso-cel-treated Analysis Set

System Organ Class Preferred Term	Number (%) of Subjects N=88
Subjects with any liso-cel-related serious TEAEs	**34 (38.6)**
Immune system disorders	21 (23.9)
Cytokine release syndrome	21 (23.9)
Nervous system disorders	7 (8.0)

Encephalopathy	2 (2.3)
Psychiatric disorders	7 (8.0)
Confusional state	5 (5.7)
Mental status changes	2 (2.3)
Metabolism and nutrition disorders	3 (3.4)
Decreased appetite	2 (2.3)

Source: ADSL and ADAE.

Table 33: Applicant – LDC-related Treatment-emergent Serious Adverse Events Reported in ≥ 2 Subjects by System Organ Class and Preferred Term - Liso-cel-treated Analysis Set

System Organ Class Preferred Term	Number (%) of Subjects N=88
Subjects with any LDC-related serious TEAEs	**14 (15.9)**
Immune system disorders	5 (5.7)
Cytokine release syndrome[a]	5 (5.7)
General disorders and administration site conditions	2 (2.3)
Pyrexia	2 (2.3)

[a] Cytokine release syndrome in these 5 subjects was also considered related to liso-cel (ADSL and ADAE).
Source: ADSL and ADAE.

The Applicant's Position:

In Liso-cel-treated Analysis Set, 47/88 (53.4%) subjects had TE-SAEs of any grade, including 34 (38.6%) with TE-SAEs related to Liso-cel and 14 (15.9%) with TE-SAEs related to LDC. Most TE-SAEs were reported in 1 or 2 subjects; the most frequently reported TE-SAEs (> 2 subjects) were CRS, confusional state, and pyrexia.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 34: Applicant – Adverse Drug Reactions Reported by > 10% of Subjects - Liso-cel-treated Analysis Set

	Number (%) of Subjects N = 88		
System Organ Class Preferred Term/Grouped Term	Any Grade n (%)	Serious n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions			
Fatigue[a]	34 (38.6)	0	2 (2.3)
Edema[b]	22 (25.0)	2 (2.3)	1 (1.1)
Fever[c]	15 (17.0)	3 (3.4)	0
Chills	10 (11.4)	0	0
Immune system disorders			
Cytokine release syndrome	54 (61.4)	21 (23.9)	1 (1.1)

System Organ Class Preferred Term/Grouped Term	Number (%) of Subjects N = 88 Any Grade n (%)	 Serious n (%)	 Grade ≥ 3 n (%)
Metabolism and nutrition disorders			
Decreased appetite	18 (20.5)	2 (2.3)	4 (4.5)
Nervous system disorders			
Encephalopathy[d]	26 (29.5)	10 (11.4)	8 (9.1)
Headache	20 (22.7)	0	0
Dizziness[e]	10 (11.4)	1 (1.1)	2 (2.3)
Motor dysfunction[f]	10 (11.4)	0	0
Tremor	10 (11.4)	0	0
Gastrointestinal disorders			
Nausea	16 (18.2)	0	2 (2.3)
Diarrhoea	15 (17.0)	0	0
Abdominal pain[g]	13 (14.8)	0	3 (3.4)
Constipation	12 (13.6)	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[h]	33 (37.5)	2 (2.3)	2 (2.3)
Infections and infestations			
Infections - pathogen unspecified[i]	14 (15.9)	4 (4.5)	5 (5.7)
Upper respiratory tract infection[j]	11 (12.5)	2 (2.3)	2 (2.3)
Vascular disorders			
Hypotension[k]	13 (14.8)	0	0
Hemorrhage[l]	9 (10.2)	1 (1.1)	0
Hypertension	9 (10.2)	0	3 (3.4)
Psychiatric disorders			
Insomnia[m]	12 (13.6)	0	0
Anxiety	11 (12.5)	0	1 (1.1)
Cardiac disorders			
Tachycardia[n]	14 (15.9)	1 (1.1)	3 (3.4)
Skin and subcutaneous tissue disorders			
Rash[o]	10 (11.4)	2 (2.3)	1 (1.1)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea[p]	10 (11.4)	0	0
Cough	9 (10.2)	0	0
Renal and urinary disorders			
Renal failure[q]	13 (14.8)	0	0

a. Fatigue includes asthenia, fatigue, malaise. **b.** Edema includes hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling, pleural effusion, pulmonary oedema. **c.** Fever includes pyrexia. **d** Encephalopathy includes confusional state, depressed level of consciousness, encephalopathy, lethargy, memory impairment, mental status changes,somnolence. **e.** Dizziness includes dizziness, dizziness postural, syncope, vertigo. **f.** Motor dysfunction includes fine motor skill dysfunction, muscle spasms, muscle tightness, muscular weakness. **g.** Abdominal pain includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper. **h.** Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal pain, myalgia, neck pain, pain in extremity. **i.** Grouped per high-level grouped term. **j.** Upper respiratory tract infection includes nasal congestion, rhinitis, rhinorrhoea, rhinovirus infection, upper respiratory tract infection. **k.** Hypotension includes hypotension, orthostatic hypotension. **l.** Hemorrhage includes catheter site haemorrhage, epistaxis, haematoma, haematuria, haemorrhage, haemorrhoidal haemorrhage, rectal haemorrhage. **m.** Insomnia includes insomnia, sleep disorder. **n.** Tachycardia includes atrial fibrillation, sinus tachycardia, tachycardia. **o.** Rash includes dermatitis contact, rash, rash erythematous, rash macular, rash maculo-

papular, rash pruritic. **p.** Dyspnoea includes dyspnoea, tachypnoea, wheezing. **q.** Renal failure includes acute kidney injury, blood creatinine increased.
Source: ADSL and ADAE.

The Applicant's Position:

The most common nonlaboratory adverse drug reactions (≥ 10% - in decreasing order of incidence) were CRS, fatigue, musculoskeletal pain, encephalopathy, edema, headache, decreased appetite, nausea, fever, diarrhea, infections - pathogen unspecified, tachycardia, abdominal pain, hypotension, renal failure, constipation, insomnia, upper respiratory tract infection, anxiety, chills, dizziness, motor dysfunction, tremor, rash, dyspnoea, hemorrhage, hypertension, and cough.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Adverse Events of Special Interest (AESI)

Data:

Table 35: Applicant – Treatment-emergent Adverse Events of Special Interest by Grade - Liso-cel-treated Analysis Set

AESI Category	Number (%) of Subjects N=88
CRS	54 (61.4)
Grade 1-2	53 (60.2)
Grade 3-4	1 (1.1)
Grade 5	0
iiNT	27 (30.7)
Grade 1-2	19 (21.6)
Grade 3-4	8 (9.1)
Grade 5	0
Infusion Related Reaction	2 (2.3)
Grade 1-2	2 (2.3)
Grade 3-4	0
Grade 5	0
Macrophage Activation Syndrome	0
Tumor Lysis Syndrome	2 (2.3)
Grade 1-2	0
Grade 3-4	1 (1.1)
Grade 5	1 (1.1)
Gr ≥3 infections	13 (14.8)
Grade 3-4	11 (12.5)
Grade 5	2 (2.3)
Gr ≥ 3 bacterial infections[a]	4 (4.5)
Gr ≥3 fungal infections[a]	1 (1.1)
Gr ≥3 viral infections[a]	4 (4.5)
Gr ≥3 infections – pathogen unspecified[a]	5 (5.7)
Prolonged cytopenia	35 (39.8)
SPM[b]	3 (3.4)

AESI Category	Number (%) of Subjects N=88
Grade ≥ 3	2 (2.3)
Hypogammaglobulinemia	6 (6.8)
Grade ≥ 3	0
Autoimmune disorder[b]	0

[a] Infections by pathogen are grouped by high-level group term.
[b] Based on adjudicated results.
Cytokine release syndrome is graded based on the Lee grading criteria.[40] Other AEs are graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The most severe grade is used for those AEs that occur more than once in an individual subject during the study.
Hypogammaglobulinaemia includes post-liso-cel 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, Hypogammaglobulinaemia, Immunoglobulins decreased, Selective IgA immunodeficiency, Selective IgG subclass deficiency and Selective IgM immunodeficiency.
Second malignancy includes post-liso-celliso-cel AEs in Malignancies SMQ and Pre-malignant conditions SMQ.
Autoimmune disorders include post-liso-cel liso-cel AEs with HLGT 'Autoimmune disorders' plus the additional PTs: Temporal arteritis, Granulomatosis with polyangiitis, Bechet's syndrome and Basedow's disease, Vasculitis and erythema nodosum.
Source: ADSL, ADAE and ADLABSUM.

Table 36: Applicant – Time to Onset and Time to Resolution of Treatment-emergent CRS - Liso-cel-treated Analysis Set

Parameter	Number (%) of Subjects N = 88
Time to onset of first CRS (days)[a]	
N	54
Mean (StD)	4.7 (2.44)
Median	4.0
Min, Max	1, 10
Time to resolution of first CRS (days)[b]	
N	53
Mean (StD)	4.7 (2.55)
Median	4.0
Min, Max	1, 14
Time to onset of first Grade >= 3 CRS (days)[a]	
N	1
Mean (StD)	11.0 (-)
Median	11.0
Min, Max	11, 11
Time to resolution of first Grade >= 3 CRS (days)[b]	
N	0

[a] Time to onset is calculated from the latest liso-cel infusion to the first onset of a CRS event.
[b] Any CRS events stop/start within 7 days (start date-stop date ≤ 7) were considered to be a single episode. Time to resolution is defined as the number of days from onset to when the last CRS event of the first episode ended. Subjects with an unresolved events in the episode are excluded from the summary.
Source: ADSL and ADTTES

Table 37: Applicant – Time to Onset and Time to Resolution of Treatment-emergent Investigator-Identified Neurological Toxicity - Liso-cel-treated Analysis Set

Parameter	Total N=88
Time to onset of first NT (days)[a]	
N	27
Mean (StD)	8.4 (5.34)
Median	8.0
Min, Max	1, 25
Time to resolution of first NT (days)[b]	
N	26
Mean (StD)	11.0 (11.89)
Median	5.0
Min, Max	1, 45
Time to onset of first Grade >= 3 NT (days)[a]	
N	8
Mean (StD)	10.0 (7.48)
Median	8.5
Min, Max	2, 27
Time to resolution of first Grade >= 3 NT (days)[b]	
N	8
Mean (StD)	11.3 (11.74)
Median	5.5
Min, Max	2, 34

[a] Time to onset is calculated from the latest liso-cel infusion to the first onset of a NT event.
[b] Any NT events stop/start within 7 days (start date-stop date ≤ 7) will be considered in a single episode. Time to resolution of NT is defined as the number of days from onset to when the last NT event of the first episode ends. Subjects with an unresolved event in the episode are excluded from the summary.
Source: ADSL and ADTTES

CRS

The Applicant's Position:

All CRS events occurred within 30 days post-infusion, with a median time to onset of 4 days (range, 1-10 days) and a median time to resolution of 4 days (range, 1-14 days). CRS was mild to moderate in severity (Grade 1-2) in the majority of the subjects (60.2%). One subject (1.2%) experienced a Grade 4 CRS which was ongoing at the time of death due to TLS. No Grade 5 CRS was reported.

The FDA's Assessment:

The FDA agrees with the Applicant position. The incidence and toxicity grades of CRS were similar in subjects included in the efficacy population (i.e., who received the recommended liso-cel dose) and in the total safety population.

Neurologic toxicity (specific to the product class)

The Applicant's Position:

iiNT was defined as Investigator-identified CNS TEAE that is reported as related to liso-cel and considered by the Investigator to be the unique clinical syndrome of NT

secondary to immune effector cell therapies from the SOCs of Nervous System Disorders and Psychiatric Disorders.

All iiNT events occurred within 60 days post-infusion, with a median time to onset of 8 days (range, 1-25 days) and a median time to resolution of 5 days (range, 1-45 days). The majority (21.6%) of iiNT AEs were mild to moderate in severity (Grade 1-2). One subject (1.2%) experienced a Grade 2 iiNT which was ongoing at the time of death due to disease progression on Day 12. No Grade 5 iiNT events were reported.

The FDA's Assessment:

Narratives were reviewed for events of iiNT. There were two cases of grade 1 neurological symptoms assessed by the Applicant as not related to liso-cel, but considered by the FDA as possibly related as described below:

Subject (b) (6) experienced events of Grade 1 loss of proprioception and Grade 1 gait disturbance on Day 7. Both events were ongoing at the time of the subject's death. The Grade 1 loss of proprioception (considered by the Applicant as not related to liso-cel/LDC/study procedure) and not considered to be an iiNT by the investigator and Grade 1 gait disturbance (not considered related to liso-cel/LDC/study procedure). No treatment was reported for either event. Neither event was considered an iiNT event or related to liso-cel; the etiology was unknown. The clinical reviewer determined that regardless of capturing these events as iiNTs or not, there would be no impact on the overall safety profile.

On Day 10, Subject (b) (6) experienced a one-day episode of Grade 1 dysarthria and Grade 1 aphasia (both not related to liso-cel/lymphodepleting chemotherapy/study procedure, no MMSE was performed), which were both not considered to be iiNT by the investigator. The clinical reviewer accepted assessment and determined no impact on the overall safety profile.

Serious Infections

The Applicant's Position:
The most frequent categories of Grade ≥ 3 infections were unspecified pathogen (5.7%) and bacterial and viral (4.5%, each).

The FDA's Assessment:

The FDA agrees with the Applicant's summary. There were five deaths due to infection (four due to Covid-19 and one due to cryptococcal meningitis). See Table 30 for further details.

Hypogammaglobulinemia

The Applicant's Position:
The frequency of hypogammaglobulinemia was low during the treatment-emergent periods (6.8%). All events were mild to moderate (Grade 1-2). See Section 6 for laboratory values of IgG levels < 500 mg/dL.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Macrophage Activation Syndrome

The Applicant's Position: No cases of MAS were reported.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Infusion Related Reaction

The Applicant's Position:
The frequency of IRR was low (2.3%), all of the IRR events were mild to moderate (Grade 1-2), and 1 event was an SAE.

The FDA's Assessment:

The FDA agrees with the Applicant's summary.

Tumor Lysis Syndrome

The Applicant's Position:
Overall, the frequency of TLS was low (2.3%). TLS occurred in 2 subjects: 1 subject had a Grade 3 event (related to liso-cel/LDC) which was ongoing at time of death from disease progression. Another subject with high tumor burden before infusion experienced a Grade 5 SAE TLS event (related to liso-cel).

The FDA's Assessment:

The FDA agrees that there were 2 events of tumor lysis syndrome among subjects who received conforming product. 1 event was Grade 3 and ongoing at time of death due to disease progression. In brief, this subject on Day 1 was diagnosed with Grade 4 events of enterococcal bacteremia and staphylococcal bacteremia (both related to LDC; not related to liso-cel/study procedure). The subject also had an event of Grade 2 CRS (resolved on Day 3). The subject had an MRI which was abnormal, consistent with lymphoma and leptomeningeal disease. The subject received subsequent anticancer treatment with hydroxyurea from Day 9 to Day 11. On Day 12 (b) (6) , the subject died due to disease progression. An autopsy was not performed. The second event of TLS was fatal (Refer to Section 8.2.4. Safety for details).

Second Primary Malignancy

The Applicant's Position:
The incidence of SPM AESIs during the treatment-emergent period was low (3.4%). None of the SPMs was of hematopoietic origin and none was considered related to liso-cel.

The FDA's Assessment:

There were 16 SPMs, one event of MDS, with the remainder of SPMs not of hematopoietic or T cell origin. None of the SPMs were assessed as related to product by the Applicant.

Across both the treatment and posttreatment periods, there was a total of 15 out of 88 subjects with one or more SPMs. None of the SPMs were considered related to liso-cel, and one in the post treatment-emergent period (myelodysplastic syndrome), was considered related to LDC. Three cases occurred in the treatment-emergent period, and 13 occurred in the post treatment-emergent period.

In the treatment-emergent period, 3 subjects had 1 or more SPMs, types listed below:

- squamous cell carcinoma,
- acinar cell carcinoma of pancreas, and
- basal cell carcinoma

During the posttreatment-emergent period, 13 subjects experienced a SPM, types listed below:

- myelodysplastic syndrome (1 event, related to LDC)
- squamous cell carcinoma of skin (5 events)
- small cell lung cancer (1 event)
- basal cell carcinoma (5 events)
- invasive ductal breast carcinoma (1 event)
- lung adenocarcinoma (1 event)
- prostate cancer (2 events)

During the posttreatment-emergent period, 2 subjects had 2 or more events, each of those 2 subjects had squamous cell carcinoma and basal cell carcinoma.

Subject (b) (6) Myelodysplastic syndrome (MDS) on Day 201 after liso-cel treatment

This was a 62-year-old-female with r/r MCL with 5 prior lines of therapy who developed grade 4 MDS 201 days after treatment with liso-cel. Per Applicant, the subject presented to an urgent care with worsening right lower extremity pain, worsening pancytopenia with neutropenia, and was confirmed to have therapy related MDS with a bone marrow biopsy. There was no evidence of MCL progression. However, the subject died on day 320 due to disease progression, and the event of MDS was ongoing at the time of death. No information on testing for presence of CAR transgene in bone marrow was provided. The Applicant considered the event of MDS related to LDC and not related to liso-cel. Although the review team acknowledges the risk of therapy related

MDS in this heavily pretreated subject, the contribution of liso-cel in development of MDS cannot be ruled out.

Prolonged Cytopenia

The Applicant's Position:
Prolonged cytopenias, defined as any Grade ≥ 3 laboratory result of decreased hemoglobin, ANC, or platelets at the Day 29 Visit, occurred in 39.8% of the subjects. Of the subjects with Grade ≥ 3 cytopenias at Day 29 who had laboratory results after Day 29, the majority recovered to Grade ≤ 2 by Month 2 (ADSL and ADLABSUM).

The FDA's Assessment:

To provide a more granular description of prolonged cytopenias, the review team's analysis was conducted by cell type. Prolonged cytopenia was defined as Grade 3 or higher cytopenias not resolved by study day 29 visit, based on laboratory results of low hemoglobin, absolute neutrophil count decreased, and platelet count decreased. A total of 21 subjects (24%) experienced prolonged Grade ≥ 3 decreased absolute neutrophil count at the Day 29 visit. A total of 28 subjects (32%) experienced Grade ≥ 3 decreased platelet count at the Day 29 visit. A total of 6 subjects (7%) experienced Grade ≥ 3 decreased hemoglobin.

Table 38. Prolonged Cytopenia Following Treatment With Liso-cel in Study 017001 MCL Cohort (N=88)

PARAMCD	All Grade, N	All Grade, %	Grade 3 or Higher, N	Grade 3 or Higher, %
Hemoglobin decreased	77	88%	6	7%
Neutrophil decreased	75	85%	21	24%
Platelet decreased	77	88%	28	32%

Source: FDA analysis of ADLBLDC dataset from study 017001 MCL Cohort

Dropouts and/or Discontinuations Due to Adverse Effects

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

The FDA's Assessment:

Not applicable.

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

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

The FDA's Assessment:

Not applicable.

Laboratory Findings

Data:

Table 39: Applicant - Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Subjects Treated with Liso-cel

Laboratory Abnormality	Grade 3 or 4 (%)
Neutrophil count decreased	67.0
White blood cell decreased	42.0
Platelet count decreased	30.7
Anemia	27.3
Lymphocyte count decreased	13.8
Hyperuricemia	11.4

Source: ADSL and ADLB

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 88 R/R MCL subjects who were treated with liso-cel. The evaluable number for each lab, rather than the total number of the safety population, were used as denominator during calculation of frequencies. FDA analysis included all subjects with a baseline and at least one post treatment value. Baseline lab values were assessed prior to lymphodepleting chemotherapy. Subjects must have had at least one grade worsening on study to be counted in the analysis, and only worse grade lab abnormality was included in our analysis. Of note, the above method of analyzing lab shift may potentially underestimate the true incidence of lab abnormalities in subjects without a baseline value, especially for labs that are not routinely done at baseline (e.g., uric acid, coagulation profile, etc.) Therefore, the review team also included subjects who had a missing pretreatment baseline laboratory toxicity grade but had an abnormal post-treatment toxicity grade as treatment-emergent laboratory abnormality. The analysis of lab abnormalities was limited to a window of 90 days post treatment with LDC/liso-cel.

Table 40 summarizes the treatment emergent lab shift abnormalities.

Table 40. FDA Analysis of Lab Abnormalities Occurring in R/R MCL Subjects Treated With Liso-cel in Study 017001 MCL Cohort N=88*

PARAMCD_FDA	Evaluable Number, N	All Grade, N	All Grade, %	Grade 3 or Higher, N	Grade 3 or Higher, %
White blood cell decreased	88	81	92%	65	74%
Neutrophil decreased	88	80	91%	71	81%
Lymphocyte decreased	88	77	88%	73	83%
Hemoglobin decreased	88	65	74%	28	32%
Platelet decreased	88	62	70%	30	34%
Calcium increased	88	50	57%	3	3%
Albumin decreased	88	46	52%	0	0%
Sodium decreased	88	28	32%	8	9%
AST increased	88	24	27%	3	3%
ALT increased	88	23	26%	2	2%
Magnesium increased	87	20	23%	2	2%
Potassium decreased	88	18	20%	3	3%
Sodium increased	88	11	13%	0	0%
White blood cell increased	88	6	7%	6	7%
Potassium increased	88	6	7%	2	2%
Neutrophil increased	88	5	6%	5	6%
Platelet increased	88	5	6%	5	6%
Lymphocyte increased	88	4	5%	1	1%
Fibrinogen decreased	80	1	1%	1	1%

Source: FDA Analysis of ADLB dataset from Study 017001 MCL Cohort
*Denominator ranges from 87-88 and reflects those patients who had both pre and post treatment laboratory values available
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDA, US Food and Drug Administration; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

Vital Signs

The Applicant's Position:

Temperature, respiratory rate, heart rate, blood pressure, and SaO2 by pulse oximetry were collected in Study 017001. There were no notable shifts in vital signs during the study. Abnormal vital signs values, including pyrexia, hypotension, or hypoxia, were mainly associated with events of CRS. Abnormal values were reported as AEs when considered clinically relevant by the investigator.

The FDA's Assessment:

FDA agrees with Applicant's position.

Electrocardiograms (ECGs)

The Applicant's Position:

ECGs were performed as a pre-treatment evaluation.

The FDA's Assessment:

FDA agrees with Applicant's position.

Immunogenicity
The Applicant's Position:
Due to the low incidence of ATA (Section 6), the relationship between ATA status and efficacy, safety, or PK was not conclusive.

The FDA's Assessment:

Refer to clinical pharmacology memo.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
No new safety concerns were identified as a result of the safety review of liso-cel 50 or 100 x 10^6 CAR+ T cells dose.

The FDA's Assessment:

FDA agrees with Applicant's position.

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:
No clear differences in rates of overall TEAEs, Grade ≥ 3 TEAEs, or AESIs were observed between subgroups for age (< 65 years vs ≥ 65 years), sex (male vs female), race (white vs other), or CNS disease status (with involvement of CNS by lymphoma at time of liso-cel treatment vs without involvement).

The FDA's Assessment:

The FDA agrees with the Applicant's summary.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Study GC-LTFU-001 is a LTFU study in all pediatric and adult subjects exposed to gene-modified T-cell therapy in company-sponsored, or company alliance partner-sponsored trials in accordance with Health Authorities' guidance for subjects treated with gene therapy products.

Safety data (AEs, deaths) from Study GC-LTFU-001 in subjects who were previously treated with liso-cel were integrated with the parent study in the ISS, per the ISS SAP.

The FDA's Assessment:

FDA agrees with the Applicant's plan.

8.2.9. Additional Safety Explorations

Side-by-side Comparison of Safety in R/R MCL and 2L/3L LBCL Populations
Data:

Table 41: Applicant – Overall Summary of Safety - Study 017001 MCL Cohort and Total 2L/3L LBCL

	Number (%) Subjects	
Safety Parameter	**R/R MCL Total N=88**	**3L+ LBCL + 2L LBCL Total N=418**
Deaths occurred after the first liso-cel infusion	46 (52.3)	143 (34.2)
Primary cause of death[a]		
Disease progression	29 (33.0)	116 (27.8)
Adverse event	5 (5.7)	14 (3.3)
COVID-19	7 (8.0)	5 (1.2)
Unknown	1 (1.1)	4 (1.0)
Other[b]	4 (4.5)	4 (1.0)
Subjects with any TEAE	88 (100)	412 (98.6)
Grade ≥3	76 (86.4)	337 (80.6)
Grade 5	4 (4.5)	13 (3.1)
Serious	47 (53.4)	176 (42.1)
LDC-related TEAEs	74 (84.1)	352 (84.2)
Liso-cel-related TEAEs	77 (87.5)	329 (78.7)
Liso-cel-related Grade ≥3	43 (48.9)	178 (42.6)
Liso-cel-related Grade 5	3 (3.4)	8 (1.9)
Liso-cel-related SAE	34 (38.6)	121 (28.9)
AESIs[c]		
CRS	54 (61.4)	190 (45.5)
Grade 1-2	53 (60.2)	177 (42.3)
Grade 3-4	1 (1.1)	12 (2.9)
Grade 5	0	1 (0.2)
Serious	21 (23.9)	69 (16.5)
iiNT	27 (30.7)	136 (32.5)
Grade 1-2	19 (21.6)	94 (22.5)
Grade 3-4	8 (9.1)	39 (9.3)
Grade 5	0	3 (0.7)
Serious	11 (12.5)	49 (11.7)
Prolonged Cytopenia (at Day 29)[c]	35 (39.8)	157 (37.6)
Grade ≥ 3 infection	13 (14.8)	50 (12.0)
Grade 5 Infection	2 (2.3)	6 (1.4)
Any-grade MAS/HLH	0	1 (0.2)

Safety Parameter	Number (%) Subjects R/R MCL Total N=88	 3L+ LBCL + 2L LBCL Total N=418
Any-grade IRR	2 (2.3)	3 (0.7)
Any-grade TLS	2 (2.3)	2 (0.5)
Treatment-emergent Period		
Any-grade SPM[d]	3 (3.4)	5 (1.2)
Any-grade Hypogammaglobulinemia	6 (6.8)	47 (11.2)
Any-grade Autoimmune Disorders[d]	0	1 (0.2)

[a] Includes deaths in Study GC-LTFU-001. [b] Deaths due to cause "Other" include GVHD, respiratory failure of unknown origin, motor vehicle accident, complications from lung cancer and failure to thrive (ADSL and ADDD).
[c] Prolonged cytopenia was defined for the MCL Cohort as any Grade ≥ 3 laboratory result of decreased hemoglobin, ANC, or platelets at the Day 29 Visit. Visit considered 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 LBCL studies. [d] Based on adjudicated results.
Source: ADSL, ADAE, ADDD and ADTTES.

The Applicant's Position:
Safety data for the R/R MCL Liso-cel-treated Analysis Set from Study 017001 were consistent with the known liso-cel safety profile for R/R LBCL Treated Set (comprised of Studies 017001 DLBCL Cohort for 3L+ LBCL, BCM-003 Arm B, and 017006 for 2L LBCL). No new safety concerns were identified. The types and frequencies of AESIs were as expected. Despite the majority of subjects were treated during the ongoing SARS-CoV-2 pandemic, the incidence of COVID-19-related AEs in the R/R MCL population was low and did not impact the overall safety profile. The types and frequencies of AESIs were as expected.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Human Carcinogenicity or Tumor Development
The Applicant's Position:
There have been no confirmed T-cell, or other hematologic, vector-mediated malignancies reported/identified, to date.

The FDA's Assessment:

Not applicable.

Human Reproduction and Pregnancy
The Applicant's Position:
There is no new information to report for liso-cel.

The FDA's Assessment:

Not applicable.

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, 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 safety concern that negatively impacted the current benefit-risk balance of liso-cel in currently approved indications.
The identified and potential risks of liso-cel are adequately addressed in the current product labeling and through the REMS Program, and no additional risk-minimization measures are considered necessary at this time.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
No new safety concerns were identified with liso-cel monotherapy in R/R MCL population.
The types and frequencies of AESIs were as expected. The majority of reported AESIs were mild to moderate in severity and manageable with protocol-specified guidelines and/or local standard of care.
The frequency of AESIs was generally similar between the R/R MCL (N = 88) and the 3L+ LBCL + 2L LBCL (N = 418) sets, including the incidences of iiNT (30.7% vs 32.5%) and prolonged cytopenia (39.8% vs 37.6%). CRS occurred at a higher frequency in the R/R MCL population (61.4% vs 45.5%) but this difference was largely driven by higher frequency in Grade 1-2 events (60.2% vs 42.3%) with no difference in Grade 3-4 events

(1.1% vs 2.9%). There was a low incidence of TLS and IRR and no report of HLH/MAS or autoimmune disorders in the R/R MCL Treated Set.
The totality of the safety data from 88 MCL subjects from Study 017001 treated with liso-cel demonstrate that the safety profile is manageable with established guidelines and consistent with those previously observed in 3L+ and 2L LBCL. The overall exposure to liso-cel is considered adequate to support characterization of its safety profile in subjects with MCL.

The FDA's Assessment:

The FDA agrees with the Applicant'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 966 patients with various histologies treated with liso-cel (See Table 42).

Table 42: FDA's Integrated Safety Analysis of Liso-cel in Studies for Hematologic Malignancies

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

Source: FDA analysis of ISS ADSL dataset
[a] includes 2L LBCL from study 017006 and BCM-003, and 3L+ LBCL from study 017001, 017007 and BCM-001
Abbreviations: CLL, chronic lymphocytic leukemia; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

Basic Demographics and Disease Features

Baseline demographics and disease characteristics of the pooled safety population is shown in Table 43.

Table 43. FDA Analysis of Baseline Demographics and Disease Characteristics of the Pooled Safety Population (N=966)

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

Source: FDA analysis of ISS ADSL and ADBASE data
Abbreviation: ECOG, Eastern Cooperative Oncology Group; PS, Performance status/score.

Safety Results

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

Deaths

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

Table 44: FDA Analysis of Deaths in the Integrated Safety Analysis Set (N=966)

Parameter	2L and 3L+ DLBCL N= 582 n (%)	CLL/SLL N= 118 n (%)	FL N=130 n (%)	MCL N=88 n (%)	MZL N=48 n (%)
All deaths	231 (40)	44 (37)	12 (9)	46 (52)	3 (6.3)
Disease progression	183 (31)	26 (22)	6 (5)	29 (33)	2 (4)
Adverse Events	23 (4)	6 (5)	3 (2)	9 (10)	1 (2)
Other causes	18 (3)	12 (10)	3 (2)	7 (8)	0
Unknown	7 (1)	0	0	1 (1)	0
Fatal AEs ≤ 30 days after liso-cel infusion	6 (1)	3 (2.5)	1 (1)	1 (1)	0
Fatal AEs > 30 days after liso-cel infusion	17 (3)	3 (2.5)	2 (1.5)	8 (9)	3 (6)

Source: FDA analysis of ISS ADSL dataset
[a] includes 2L LBCL from study 017006 and BCM-003; and 3L+ LBCL from study 017001, 017007 and BCM-001
Abbreviations: AE, adverse event; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; 2L, second line; 3L, third line.

Table 45 summarizes the most common AEs in ISS.

Table 45. FDA Analysis of Most Common Adverse Events in Integrated Analysis Set (N=956)

MedDRA PT	3L+ LBCL (n=429) All Grade %	3L+ LBCL (n=429) ≥G3 %	2L LBCL (n=148) All Grade %	2L LBCL (n=148) ≥G3 %	CLL/ SLL (n=118) All Grade %	CLL/ SLL (n=118) ≥G3 %	FL (n=127) All Grade %	FL (n=127) ≥G3 %	MCL (n=88) All Grade %	MCL (n=88) ≥G3 %	MZL (n=46) All Grade %	MZL (n=46) ≥G3 %
Cytokine release syndrome	44.5	3.3	45.9	1.4	84.7	8.5	58.3	0.8	62.5	1.1	73.9	2.2
Headache	27.7	0.9	23.6	3.4	30.5	0.8	29.1	0.0	22.7	0.0	21.7	2.2
Constipation	22.8	0.2	17.6	1.4	26.3	0.0	19.7	0.0	14.8	0.0	2.2	0.0
Fever	24.7	0.0	15.5	0.0	29.7	0.8	18.9	0.0	18.2	0.0	17.4	0.0
Diarrhea	25.6	1.6	17.6	0.0	30.5	1.7	17.3	0.0	17.0	0.0	28.3	2.2
Fatigue	37.1	1.6	31.8	0.0	36.4	6.8	14.2	0.0	34.1	2.3	19.6	2.2
Tremor	13.5	0.7	12.8	0.7	24.6	1.7	14.2	0.0	11.4	0.0	19.6	0.0
Asthenia	9.3	1.2	7.4	1.4	9.3	0.8	12.6	0.0	1.1	0.0	6.5	2.2
Nausea	32.4	1.2	24.3	0.7	38.1	0.0	9.4	0.0	18.2	2.3	17.4	2.2
Decreased appetite	24.5	2.8	14.9	0.7	25.4	4.2	21.6	4.5	21.6	4.5	13.0	4.3
Vomiting	18.2	0.2	10.1	0.0	14.4	0.0	4.7	0.0	5.7	0.0	6.5	0.0
Dizziness	17.9	0.5	15.5	0.0	26.3	0.0	4.7	0.0	6.8	0.0	13.0	0.0
Cough	17.5	0.0	10.8	0.0	17.8	0.0	7.1	0.0	10.2	0.0	6.5	0.0
Hypotension	16.8	2.8	14.9	1.4	19.5	0.8	7.9	0.0	13.6	0.0	13.0	0.0
Hypogammaglobulinemia	16.6	0.2	7.4	0.7	15.3	2.5	2.4	0.0	11.4	0.0	4.3	2.2
Peripheral edema	15.4	0.7	12.2	0.0	16.1	0.0	4.7	0.0	17.0	1.1	2.2	0.0
Abdominal pain	14.5	1.9	7.4	1.4	18.6	0.0	7.1	0.8	9.1	2.3	6.5	0.0
Febrile neutropenia	12.6	12.4	7.4	7.4	15.3	15.3	6.3	4.7	6.8	5.7	6.5	6.5
Confusional state	12.6	1.9	7.4	2.0	27.1	9.3	2.4	0.8	15.9	2.3	10.9	2.2
Insomnia	12.4	0.2	12.8	0.0	18.6	0.8	5.5	0.0	12.5	0.0	4.3	0.0
Arthralgia	11.2	0.5	10.8	1.4	11.0	0.0	7.9	0.0	11.4	0.0	8.7	0.0
Back pain	11.0	0.9	8.8	0.0	12.7	0.8	7.9	0.8	15.9	1.1	4.3	0.0
Sinus tachycardia	11.0	0.0	6.1	0.0	11.0	0.8	4.8	0.0	10.2	1.1	4.3	0.0
Dyspnea	10.7	0.5	8.8	1.4	20.3	5.9	0.8	0.0	9.1	0.0	8.7	0.0
Anxiety	8.9	0.0	4.7	0.7	14.4	0.8	1.6	0.0	13.6	1.1	6.5	0.0
Chills	8.4	0.0	6.8	0.0	18.6	0.8	3.1	0.0	11.4	0.0	10.9	0.0
Hypertension	8.9	2.6	9.5	4.7	14.4	5.9	4.7	1.6	10.2	3.4	6.5	4.3
Upper Resp Tract Infection	3.5	0.5	2.0	0.0	5.9	0.8	3.1	0.0	10.2	2.3	2.2	0.0
Pain in Extremity	7.7	0.5	6.8	1.4	7.3	0.9	2.4	0.0	10.2	1.1	4.3	0.0

MedDRA PT	3L+ LBCL (n=429) All Grade %	3L+ LBCL (n=429) ≥G3 %	2L LBCL (n=148) All Grade %	2L LBCL (n=148) ≥G3 %	CLL/ SLL (n=118) All Grade %	CLL/ SLL (n=118) ≥G3 %	FL (n=127) All Grade %	FL (n=127) ≥G3 %	MCL (n=88) All Grade %	MCL (n=88) ≥G3 %	MZL (n=46) All Grade %	MZL (n=46) ≥G3 %
Pleural effusion	5.4	1.2	2.7	0.0	4.2	1.7	1.6	0.0	4.5	0.0	13.0	4.3
COVID-19	2.1	0.9	3.4	2.7	2.5	0.0	3.9	1.6	4.5	4.5	10.9	4.3
Acute kidney injury	4.9	1.4	3.4	0.7	15.3	3.4	0.8	0.0	9.1	0.0	2.2	2.2
Hypoxia	4.4	1.6	2.0	1.4	14.4	10.2	1.6	0.8	3.4	1.1	4.3	2.2
Muscular weakness	5.8	1.6	5.4	2.0	12.7	2.5	1.6	0.0	8.0	0.0	0.0	0.0
Encephalopathy	6.3	3.7	2.7	1.4	11.9	8.5	0.8	0.8	5.7	3.4	0.0	0.0
Dyspepsia	4.4	0.0	2.7	0.0	11.0	0.0	3.1	0.0	1.1	0.0	4.3	0.0
Tumor lysis syndrome	0.5	0.5	0.0	0.0	11.0	11.0	0.0	0.0	2.3	2.3	2.2	0.0
Somnolence	5.8	0.7	3.4	0.7	10.2	3.4	0.8	0.0	5.7	2.3	4.3	0.0

Source: FDA analysis of ISS ADSL and ADAE data
Abbreviations: CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma; 2L, second line; 3L, third line.

For the purpose of inclusion of an integrated summary of safety under Warnings & Precautions, pooled data from currently approved indications (LBCL, CLL/SL and FL) along with MCL data were analyzed.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

As described in the efficacy results section (Section 8.1), the following issues were identified:

- FDA's differed from the PAS proposed by the Applicant. For efficacy, the FDA's PAS includes liso-cel treated patients who have received at least 2 prior lines of therapy including both a BTKi and received the planned commercial dose of 90 to 110×10^6 cells (n=68).
- While the study also assessed other endpoints such as PFS and OS, the interpretation of these time-to-event endpoints is limited in the setting of a single-arm trial. Similarly, while FDA encourages evaluation of patient reported outcomes in clinical trials of oncologic products, the assessment of these outcomes are limited in the context of single are trials and analyses are therefore not considered for regulatory decision-making.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Study 017001 MCL cohort provides substantial evidence of the effectiveness of liso-cel for the treatment of adult patients with R/R MCL who have received at least 2 prior lines of systemic therapy, including a BTK inhibitor. Study 017001 MCL cohort demonstrated an ORR of 85.3% (95% CI: 74.6, 92.7) with durability of response, with a CR rate of 67.6% (95% CI: XX,CX) in this heavily pretreated population.

- Of the 58 subjects who achieved an objective response, the median DOR was 13.3 months (95% CI, 6.0, 23.3).
- Of the subjects who achieved CR, the estimated KM rate of continued response at 12 and 18 months was 57.8% (95% CI, 41.9, 70.7) and 48.0% (95% CI, 31.6, 62.6), respectively.

The safety profile was notable for a fatal AE rate of 10% (9/88) which was numerically higher in the MCL population as compared to the overall B-cell ISS population [4% (42/966)]; however, most deaths were due to progression of disease (33%), and the rates of non-PD related deaths were similar to the ISS rate. Overall, no new safety signal was identified. This difference in fatal AE rate is potentially related to the heavily pretreated population, more aggressive underlying disease and coexisting comorbidities

due to prior therapies compared to the larger population of patients with more indolent histologies. Severe CRS and neurotoxicity rates were similar to those observed in the currently approved indications. Severe CRS and neurotoxicity are associated with liso-cel are serious and can be life-threatening and require supportive measures.

Recommendations on Regulatory Actions

The clinical review team recommends traditional approval of liso-cel for the treatment of adult patients with R/R MCL who have received at least 2 prior lines of therapy including a BTK inhibitor. The basis for the recommendation is the large magnitude of ORR and its durability, in the context of a high CRR and an acceptable risk profile. In this heavily pre-treated population, 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 recipients of the commercial product for short term and long-term toxicity was requested and agreed upon.

X X

Primary Clinical Reviewer (s)

X X

MORE Team Lead MHB Clinical Team Lead

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this BLA because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of liso-cel for the proposed indication.

10 Pediatrics

The Applicant's Position:
Not applicable; liso-cel was granted orphan drug designation for MCL and is therefore exempt from PREA requirements.

The FDA's Assessment:

Per the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments. However, Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that original marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations).

Liso-cel has orphan drug designation for MCL. CD20 is a molecular target relevant to growth or progression of pediatric cancer. However, this is a supplemental BLA seeking a new indication of liso-cel for MCL. Therefore, FDARA does not apply and this application is exempt from PREA.

11 Labeling Recommendations

Data:

Table 46: Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1. Indications and Usage	BREYANZI is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after a Bruton's tyrosine kinase (BTK) inhibitor. Limitations of Use BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.	BREYANZI is indicated for the treatment of adult patients with relapsed or refractory MCL who have received at least 2 prior lines of systemic therapy, including after a Bruton's tyrosine kinase (BTK) inhibitor. Limitations of Use BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.
2. Dosage and Administration	For MCL the dose is 90 to 110 × 10^6 CAR-positive viable T cells	Approved dose: 90 to 110 × 10^6 CAR-positive viable T cells
5. Warnings and Precautions	CRS (5.1) Neurologic Toxicities (5.2) BREYANZI REMS (5.3) Serious Infections (5.5) Prolonged Cytopenias (5.6) Hypogammglobulinemia (5.7)	Adding pooled data of CRS (5.1), Neurologic toxicities (5.2), Serious infections (5.5), Prolonged cytopenias (5.6) and hypogammaglobulinemia (5.7) from LBLC, CLL/SLL, FL and MCL studies instead of describing the studies individually.
6.1 Clinical Trials Experience (TRANSCEND-MCL Cohort)	The most common nonlaboratory adverse reactions (≥ 20%) were CRS, fatigue, musculoskeletal pain, encephalopathy, edema, headache, and decreased appetite. The most common Grade 3-4 laboratory abnormalities include neutrophil count decreased, white blood cell decreased, platelet count decreased, hemoglobin decreased, lymphocyte count decreased, and uric acid increased.	This section includes adverse reactions, and laboratory abnormalities observed in the MCL cohort of Study 017001. The safety population includes all the participants who received conforming BREYANZI product (N=88)
6.2 Immunogenicity	Update with anti-product antibody data from TRANSCEND-MCL Cohort.	Updated with data of all the participants who received conformal BRYANZI product in the MCL cohort of Study 017001
8.5 Geriatric Use	Update with data from TRANSCEND-MCL Cohort.	Adding pooled data from LBLC, CLL/SLL, FL and MCL studies instead of describing the studies individually
14 Clinical Studies	Relapsed or Refractory Mantle Cell Lymphoma (14.2)	This section is updated to include efficacy data from MCL cohort of 017001 study with the following revisions: 1. Added duration of

		responses for responders at 12 and 18 months in Table 22. 2. Added footnote in Table 22 to include median follow-up for DOR.

The Applicant's Position:
The clinical data provided in this sBLA demonstrate the clinical benefit and safety of the use of liso-cel for the treatment of adult patients with R/R MCL.

The FDA's Assessment:

The data submitted to the BLA do not support claims of effectiveness for the broader MCL population described in the Applicant's indication statement. Rather, the FDA review team revised the indication statement to reflect approval for the narrower indication "adult patients with relapsed or refractory MCL after at least two prior lines of therapy including a BTKi".

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Based on review of available data from the clinical trial, the safety concerns for liso-cel continue to warrant a REMS Program with ETASU to mitigate the risks of CRS and NT and to ensure the benefits outweigh the risks for use of the product. The Applicant submitted a REMS major modification that included revisions to the REMS materials only to address the new indication and labeling changes proposed in sBLA 125714/227.

The REMS requires hospital sites to be certified and have on-site, immediate access to tocilizumab.. Under STN 125714/227, there were no changes to the REMS Document or REMS Hospital Enrollment Form. Division of Pharmacovigilance (DPV) recommends approval of liso-cel REMS Modification under STN 125714/227.

Please see the final version of the REMS Document, REMS materials, and package insert submitted by the Applicant for the final agreed-upon content and language, including product indication and dosing. For details, please refer to OBPV/DPV reviewer's memo.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

3) FDA determined that the Sponsor will be required to conduct the following study as a postmarketing requirement (PMR) under Section 505(o) of Federal Food, Drug, and Cosmetic Act :

A postmarketing, multicenter, prospective, observational study (CA082-1093) to assess the long-term safety of lisocabtagene maraleucel and the risk of secondary malignancies occurring after treatment with lisocabtagene maraleucel. The study will include at least 300 adult patients with relapsed or refractory MCL. The enrolled patients will be followed for 15 years after the product administration.

Proposed study milestone dates:

- Final protocol submission: August 31, 2024
- Study completion date: September 30, 2044
- Final study report submission: September 30, 2045

4) Adequate testing strategies must be included in the study design for assessment of secondary malignancies. The Sponsor was requested to provide information in the final protocol on the methods to ensure sample collection of tumor samples from secondary malignancies and include the testing algorithm in the protocol.

The Sponsor acknowledged the PMR notification for Study CA082-1093 and confirmed the above-mentioned milestone dates in a response on April 30, 2024.

14 Chief, Clinical Hematology Branch

X

15 Oncology Center of Excellence (OCE) Signatory

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

X

16 Division Director (DCEH)

X

17 Appendices

17.1. FDA Grouped Terms

Table 47: FDA Grouped Terms

FDA Grouped Terms	Dictionary-Derived Term
Abdominal pain	Abdominal discomfort Abdominal distension Abdominal pain Abdominal pain upper
Renal disorder	Acute kidney injury
Delirium	Agitation Hallucination
Anemia	Anaemia
Affective disorder	Anxiety
Fatigue	Asthenia
Tachycardia	Atrial fibrillation Ventricular tachycardia Sinus tachycardia

FDA Grouped Terms	Dictionary-Derived Term
	Atrial tachycardia
Renal disorder	Blood creatinine increased
Musculoskeletal pain	Arthralgia Musculoskeletal pain Myalgia Neck pain Pain in extremity Back pain Bone pain
Fungal infection	Candida infection Oral candidiasis
Anorexia	Decreased appetite
Affective disorder	Depressed mood Depression
Thrombosis	Deep vein thrombosis Venous thrombosis Device related thrombosis
Diarrhea	Diarrhoea
Dizziness	Dizziness Dizziness postural
Skin disorder	Dry skin Flushing Pruritus
Motor dysfunction	Dysarthria Psychomotor skills impaired Muscle spasms Muscle tightness Muscular weakness Fine motor skill dysfunction Dysmetria
Gastrointestinal disorder	Anal fissure Dyspepsia Constipation Gastrooesophageal reflux disease Flatulence Diverticulitis Dysphagia
Dyspnea	Dyspnoea
Bacterial infection	Enterococcal bacteraemia
Gastroenteritis	Gastroenteritis salmonella
Hemorrhage	Epistaxis Rectal haemorrhage Catheter site haemorrhage Haematoma Haematuria Haemorrhage Haemorrhoidal haemorrhage
Renal disorder	Hydronephrosis
Fatigue	Malaise
Encephalopathy	Lethargy

FDA Grouped Terms	Dictionary-Derived Term
	Somnolence
	Memory impairment
	Mental status changes
	Confusional state
	Depressed level of consciousness
Edema	Pulmonary oedema
	Scrotal oedema
	Pulmonary oedema
	Oedema genital
	Oedema peripheral
	Periorbital oedema
	Peripheral swelling
	Pleural effusion
	Hypervolaemia
	Localised oedema
Hypotension	Orthostatic hypotension
Infections-pathogen unspecified	Periorbital cellulitis
	Skin infection
Fever	Pyrexia
Rash	Dermatitis
	Dermatitis contact
	Rash
	Rash erythematous
	Rash follicular
	Rash macular
	Rash maculo-papular
	Rash pruritic
	Rash pustular
Bradycardia	Sinus bradycardia
Dizziness	Syncope
	Vertigo
Genitourinary Disorder	Urinary incontinence
	Urinary retention
	Urinary tract pain
Dyspnea	Wheezing

Source: FDA Analysis ADAE

17.2. Additional Efficacy Analysis

Table 48. FDA Analysis of Difference for Responders in Best Overall Response (BOR) using IRC Charter versus IRC FDA Algorithm*

#	SUBJID	BOR per IRC	BOR per Applicant IRC FDA Algorithm	BOR per FDA Adjudication	Reason for Discrepancy
1	(b) (6)	PR	CR	PR	Difference in radiology PET scan assessments, FDA maintained the IRC response assessment.
2		PR	CR	PR	Difference in radiology PET scan assessments, FDA maintained the IRC response assessment.
3		CR	PR	PR	Evidence of bone marrow involvement by PET scan at baseline; no bone marrow biopsy was performed at baseline. A bone marrow biopsy to confirm CR post liso-cel infusion would have been required.
4		CR	PD	PD	Spleen response of PD; per IRC-FDA Algorithm only, spleen evaluation is incorporated into the overall response.
5		CR	PR	PR	The BOR per IRC-FDA downgraded to PR requiring a bone marrow biopsy to confirm CR post liso-cel infusion in the setting of not having a bone marrow biopsy performed at baseline.
6		CR	PR	PR	Evidence of bone marrow involvement by PET at baseline; no bone marrow biopsy was performed at baseline. A bone marrow biopsy to confirm CR post liso-cel infusion would have been required.
7		CR	PR	PR	Delayed recovery of prolonged cytopenia (ie, beyond Day 90) in the setting of no evidence of bone marrow involvement by PET at baseline and no bone marrow biopsy performed at baseline. A bone marrow biopsy to confirm CR post liso-cel infusion would have been required.
8		PR	CR	PR	Difference in radiology PET scan assessments, FDA maintained the IRC response assessment.
9		CR	CR	PR, D29 CR, D90	A bone marrow biopsy to confirm CR post liso-cel infusion would have been required at Day 29. BMB confirmed CR at Day 90.
10		PR	PD	PD	Clinical PD.
11		CR	PR	PR	A bone marrow biopsy to confirm CR post liso-cel infusion would have been required.

Source: FDA analysis of ADRS dataset, Applicant efficacy narratives, Summary of Clinical Efficacy, and JCAR017-FOL001 clinical study report.
*There were 3 non-evaluable assessments per IRC reassessed per the IRC FDA algorithm as PD, and 3 SD per IRC reassessed per the IRC FDA algorithm as PD.
** Based upon the response assessment per IRC FDA algorithm which incorporates use of BMB assessments, one subject ((b) (6)) was downgraded at Day 29 from CR to PR because there was evidence of fludeoxyglucose-18 (FDG)-avid lesions in the bone marrow at baseline, and a BMB showed 45% lymphoma cells but a post-baseline BMB at Day 29 was not collected to confirm a CR. Subsequently, a BMB was obtained at Day 90 to confirm the BOR of CR.

17.3. References

The Applicant's References: References are provided in Appendix 17.5.

The FDA's References:

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17.4. Financial Disclosure

The Applicant's Position:

A list of all investigators in Study 017001 will be provided and will include a financial disclosure package which provides the details of the process followed for collecting financial disclosures, table of investigators with disclosable interests reported by investigators, and if applicable, a table with due diligence efforts for the collection of missing financial disclosures. If/when an investigator reported disclosable financial interest, an assessment of the potential bias will be included.

The FDA's Assessment:

See Section 8.1.2.

Covered Clinical Study (Name and/or Number):* 017001

Was a list of clinical investigators provided:			Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 420			
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0			
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6			
	If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 2 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0			
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) 0			
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.

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