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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement BLA
STN	125714/90
CBER Received Date	December 23, 2021
PDUFA Goal Date	June 24, 2022
Division / Office/ Center	DCEPT/OTAT/CBER OCE
Priority Review (Yes/No)	Yes
Reviewer Names	Helkha Peredo-Pinto, M.D. (Study BCM-003) Mona Elmacken, M.D. (Study 017006)
Review Completion Date / Stamped Date	June 24, 2022
Supervisory Concurrence	Yvette Kasamon, M.D. Adnan Jaigirdar, M.D. Marc Theoret, M.D. Tejashri Purohit-Sheth, M.D.
Applicant	Juno Therapeutics
Established Name	Lisocabtagene maraleucel (JCAR017)
(Proposed) Trade Name	Breyanzi
Pharmacologic Class	CD19-directed, genetically modified autologous T cell immunotherapy
Formulation, Including Adjuvants	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 1:1 CAR-positive viable T cells of the CD8 and CD4 components, with each component supplied separately.
Dosage Form and Route of Administration	Intravenous infusion
Dosing Regimen	For large B-cell lymphoma after one line of therapy: single dose containing 90 to 110 × 10^6 CAR-positive viable T cells administered by IV infusion and preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.
Applicant Proposed Indications/ Intended Populations	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: • after failure of first-line therapy in patients who are candidates for hematopoietic stem cell transplant (HSCT); or • with relapsed or refractory disease in patients for whom HSCT is not intended Limitations of Use: Not indicated for the treatment of

	patients with primary central nervous system lymphoma
Recommendation on Regulatory Action	Regular approval
Recommended Indications/ Intended Populations	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; 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 Limitations of Use: Not indicated for the treatment of patients with primary central nervous system lymphoma
Orphan Designated (Yes/No)	Yes

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GLOSSARY

Abbreviation	Definition
1L	First-line
2L	Second-line
3L	Third-line
AESI	Adverse event of special interest
ASCT	Autologous stem cell transplantation
AUC	Area under the curve
BEAM	BCNU (carmustine), etoposide, cytarabine, and melphalan
BOR	Best overall response
CAR-T	Chimeric antigen receptor T cell
CI	Confidence interval
CMC	Chemistry, manufacturing, and controls
CMR	Complete metabolic response
CNS	Central nervous system
Cox-PH	Cox-proportional hazards
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
ddPCR	Droplet digital polymerase chain reaction
DHL/THL	Double/triple hit lymphoma
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffuse capacity of the lung for carbon monoxide
DMSO	Dimethyl sulfoxide
DoCR	Duration of complete response
DOR	Duration of response
DSMB	Data safety monitoring board
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic Common Technical Document
eCRF	Electronic case report form
EFS	Event-free survival
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer – Quality of Life C30 Questionnaire
EQ VAS	European Quality of Life visual analogue scale
EuroQol	European Quality of Life
FACT-LymS	Functional Assessment of Cancer Therapy-Lymphoma Subscale
FL	Follicular lymphoma
FL3B	Follicular lymphoma Grade 3B
GCB	Germinal center B-cell-like
HCT-CI	Hematopoietic cell transplantation specific comorbidity index
HDCT	High-dose chemotherapy
HGBL	High-grade B-cell lymphoma
HR	Hazard ratio

HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
IA	Interim analysis
ICANS	Immune effector cell-associated neurotoxicity syndrome
IPD	Important Protocol Deviation
IRC	Independent review committee
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent to treat
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
LFTU	Long-term follow-up
Liso-cel	Lisocabtagene maraleucel
LOU	Limitations of use
MAS/HLH	Macrophage activation syndrome/hemophagocytic lymphohistiocystosis
MedDRA	Medical Dictionary for Regulatory Activities
NALT	New anti-lymphoma therapy
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NOS	Not otherwise specified
NR	Not reached
NT	Neurologic toxicity
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
Pd	Pharmacodynamics
PD	Progressive disease
PFS	Progression-free survival
PFS-2	PFS on next line of treatment
PK	Pharmacokinetic
PMBCL	Primary mediastinal large B-cell lymphoma
PP	Per protocol
PMR	Postmarketing requirement
PR	Partial response
PREA	Pediatric Research Equity Act
PRO	Patient-reported outcome
PT	Preferred term
R-CHOP	Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone
R-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
R-GDP	rituximab, gemcitabine, dexamethasone, and cisplatin
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
RCL	Replication-competent lentivirus
R/R	Relapsed or refractory
REMS	Risk evaluation and mitigation strategy

RMS/BLA	Regulatory management system for the biologics license application
sAAIPI	Secondary age-adjusted International Prognostic Index
SAE	Serious adverse event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
scFv	Single-chain variable fragments
SD	Stable disease
SOC	System organ class
SPM	Second primary malignancy
StD	Standard Deviation
TEAE	Treatment-emergent adverse event
THRBCL	T cell/histiocyte-rich large B-cell lymphoma

1. EXECUTIVE SUMMARY

The clinical review team recommends regular approval of lisocabtagene maraleucel for the treatment of adult patients with large B-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 1) refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or 2) 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. As limitations of use (LOU), lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

This is an extension of the existing indication in adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy, 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, which received regular approval on February 5, 2021.

Lisocabtagene maraleucel is a CD19-directed genetically modified autologous cellular immunotherapy consisting of autologous T cells that have been transduced with a lentiviral vector encoding an anti-CD19, CD28/4-1BB chimeric antigen receptor (CAR). The recommended dose for the second-line indication is a single IV infusion of 90-110 x 10^6 CAR-positive T cells, preceded by fludarabine and cyclophosphamide for lymphodepletion.

Conclusions on the Substantial Evidence of Effectiveness

Two adequate and well-controlled studies support the second-line indications for lisocabtagene maraleucel, both evaluating a single infusion of lisocabtagene maraleucel, preceded by lymphodepleting chemotherapy, for relapsed or refractory LBCL after one line of chemoimmunotherapy. Study BCM-003, is a randomized open-label Phase 3 study comparing standard therapy versus (vs.) lisocabtagene maraleucel in transplant-eligible patients, and Study 017006, a single-arm, Phase 2, multicenter study in transplant-ineligible patients.

Study BCM-003 (TRANSFORM)

BCM-003 is a Phase 3, randomized, open label, multicenter trial intended for second-line therapy of LBCL in patients who are eligible for autologous HSCT. The study randomized 184 subjects in a 1:1 ratio to either a single infusion of lisocabtagene maraleucel (preceded by lymphodepleting chemotherapy) or to standard therapy. All subjects had either primary refractory disease or relapsed within 12 months of completing first-line therapy, were potentially eligible for autologous HSCT, and had not yet received second-line treatment. Standard therapy consisted of protocol-defined, platinum-based chemoimmunotherapy for three cycles followed by high-dose chemotherapy (HDCT) and autologous HSCT in patients who achieved at least partial response (PR). Altogether, 92 subjects were randomized to each arm and 74% of the study population had primary refractory disease.

The primary efficacy measure was event-free survival (EFS) as determined by a blinded independent review committee (IRC). On interim analysis, EFS was statistically

significantly improved for the lisocabtagene maraleucel arm compared to the standard therapy arm, with a stratified hazard ratio (HR) of 0.34 (95% CI:0.22, 0.51; one-sided p-value <0.0001). The estimated median EFS in the lisocabtagene maraleucel arm was 10.1 months (95% CI: 6.1, NR) compared to 2.3 months (95% CI: 2.2, 4.3) in the standard therapy arm. The estimated 1-year EFS was 45% (95% CI: 29, 59) and 24% (95% CI: 14, 35), respectively.

The IRC-assessed complete response (CR) rate was statistically significantly higher at 66% (95% CI: 56, 76) in the lisocabtagene maraleucel arm compared to 39% (95% CI: 29, 50) in the standard therapy arm (one-sided p-value = 0.0001). IRC-assessed progression-free survival (PFS) was also statistically significantly improved in the lisocabtagene maraleucel arm (estimated median: 14.8 months vs. 5.7 months, respectively; one-sided p-value = 0.0001).

Study 017006 (PILOT)

The efficacy of lisocabtagene maraleucel was evaluated in a single-arm, open-label, multicenter trial (PILOT) in patients with primary refractory or relapsed LBCL after first-line chemoimmunotherapy. The study enrolled patients who were not eligible for high-dose chemotherapy and autologous HSCT due to age, poor performance status or comorbidities, while also having adequate organ function for CAR-T cell therapy.

In recipients of lisocabtagene maraleucel (61 patients, of 74 who underwent leukapheresis), ORR was 80% with a CR rate of 54% (95% CI: 41, 67). Among the 33 subjects achieving CR, the estimated rate of continued response was 83% (95% CI: 64 to 93) at 6 months and 68% (95% CI: 45 to 83) at 12 months. By intention-to-treat analysis, ORR was 68% with a CR rate of 46% (95% CI: 34, 58).

Safety

Cytokine release syndrome (CRS) and neurologic toxicities are leading toxicities of lisocabtagene maraleucel that carry a boxed warning, with a risk evaluation and mitigation strategy (REMS) that includes elements to assure safe use (ETASU). The safety profile in the two studies above was consistent with the safety profile described previously in the later-line setting. Of the 150 recipients combined who received lisocabtagene maraleucel after one line of therapy for LBCL, CRS occurred in 45% including Grade 3 CRS in 1.3% of subjects. Neurologic toxicities occurred in 27% (41/150) of subjects, including Grade 3 cases in 7% of subjects. Serious adverse reactions occurred in 33% to 38% of subjects.

In conclusion, two adequate and well-controlled studies provide substantial evidence of efficacy of lisocabtagene maraleucel in patients with primary refractory LBCL or first relapse of LBCL who currently have limited satisfactory treatment options. Accelerated approval and regular approval are considerations for the tumor-based outcomes in these studies. The magnitude of clinical benefit demonstrated with lisocabtagene maraleucel on the following tumor-based outcomes supports regular approval: Study BCM-003 demonstrates clinical benefit through clinically meaningful improvements in EFS and PFS, while Study 017006 demonstrates clinically significant CR rates and the potential for durable CRs in a difficult-to-treat patient population. Given the life-threatening nature of the disease, the toxicities are acceptable.

1.1 Demographic Information

Of the 150 subjects combined who received lisocabtagene maraleucel as second-line

treatment of LBCL, 89 (59%) were at least 65 years of age. In Study BCM-003, the median age of the lisocabtagene maraleucel-treated population was 59 years (range: 20 to 74 years), 47% were male, 58% were white, 11% were Asian, and 5% were black. In Study 017006, of the 61 patients who received lisocabtagene maraleucel, the median age was 74 years (range: 53 to 84 years), 61% were male, 89% were white, 3% were Asian, and 2% were black.

1.2 Patient Experience Data

Health-related quality of life (HRQoL) was assessed as a secondary endpoint in Study BCM-003 and Study 017006.

	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	☒ Clinical outcome assessment (COA) data, such as	
	☒ Patient-reported outcome (PRO)	6.1.11.2, 6.2.11.2
	☐ Observer-reported outcome (ObsRO)	
	☐ Clinician-reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Non-Hodgkin lymphomas (NHLs) account for approximately 4% of all new cancers and 3% of cancers related deaths in the U.S. DLBCL, which comprises 30-40% of NHLs, is fatal if not cured. Primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (FL) are typically treated along a DLBCL paradigm. Approximately half of all patients with aggressive B-cell NHL have relapsed or refractory (R/R) disease, with an estimated 10-15% of patients with DLBCL having primary refractory disease and an additional 20-30% relapsing after an initial objective response.[1] High-grade B-cell lymphomas (HGBLs) with aberrations in MYC, BCL2, and/or BCL6 ("double hit" and "triple hit" lymphomas) are associated with an inferior prognosis, even in the newly diagnosed setting,[2] and in the relapsed setting are also typically treated along a DLBCL paradigm. Patients with untreated relapsed or refractory (R/R) aggressive B-cell lymphoma have a median survival of approximately 3-4 months.

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

Standard first-line therapy for DLBCL includes cyclophosphamide, doxorubicin, vincristine, and prednisolone in combination with anti-CD20 monoclonal antibody (mAb) rituximab (R-CHOP).[3] In the second-line setting, high-dose therapy with autologous HSCT has curative potential for LBCL. In patients who are potential candidates for HSCT, second-line chemotherapy informs chemosensitivity (the ability to achieve an objective response) and the transplant decision, as patients with chemoresistant disease tend not to benefit from this procedure. In the second-line setting, only approximately 50% of patients who are potential transplant candidates are expected to reach HSCT, and relapse despite HSCT is more frequent than cure.[4]

In transplant candidates, second-line chemotherapy regimens include R-ICE (ifosfamide, carboplatin, etoposide), R-DHAP (dexamethasone, high-dose cytarabine, cisplatin), R-GDP (gemcitabine, dexamethasone, cisplatin), and R-ESHAP (etoposide, solumedrol, high-dose cytarabine, dexamethasone, cisplatin). No single regimen has demonstrated superiority in a randomized trial. Patients who respond to second-line chemotherapy and proceed to autologous HSCT have a reported 5-year EFS of 46% and overall survival (OS) of 53%.[5] In the CORAL study, among patients who received second-line chemotherapy, those with early first relapse (approximately 60% of the patients) had a 1-year EFS below 20% compared with a 50% for those who relapse after one year.[6]

There is no one universal standard for patients with primary refractory LBCL or patients who are ineligible for, or who relapse despite, HSCT.[1, 7, 8] Three CD19-directed, autologous chimeric antigen receptor (CAR) T cell therapies – axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel – have regular approval for the treatment of adult patients with R/R LBCL after two or more lines of systemic therapy. The basis for approval was complete response rate and duration of response in single-arm trials. In addition, in April 2022, axicabtagene ciloleucel received regular approval for the treatment of adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. The basis of this approval was EFS in a randomized phase 3 trial, similar to BCM-003, in which transplant-eligible patients with primary refractory LBCL or

early relapse of LBCL were randomized to receive either axicabtagene ciloleucel or standard therapy (chemotherapy followed by autologous HSCT).

For patients who are not candidates for HSCT because of comorbidities or advanced age, treatment is palliative. Less intensive chemotherapy regimens, such as gemcitabine-based regimens, can be considered, however responses tend to be short-lived. Tafasitamab in combination with lenalidomide has accelerated approval for the treatment of adult patients with R/R DLBCL, NOS, including DLBCL arising from low grade lymphoma and who are not eligible for autologous HSCT. Three other therapies have accelerated approval for the third-line or later-line setting (selinexor, polatuzumab vedotin in combination with bendamustine and rituximab, and loncastuximab tesirine-lpyl). Although axicabtagene ciloleucel has regular approval for a second-line LBCL indication, the basis for that indication was a trial, similar to BCM-003, that was restricted to transplant candidates.

2.3 Safety and Efficacy of Pharmacologically Related Products

For second-line treatment of LBCL, one pharmacologically related product – axicabtagene ciloleucel – is FDA approved (Section 2.2).

Approved CAR-T cell products have a distinct pattern of toxicity that includes infections and cytopenias but is most notable for cytokine release syndrome (CRS) and neurologic toxicity (NT). CRS and neurologic toxicity (NT) are serious adverse events associated with CAR-T therapies. CRS results from massive cytokine and chemokine release when CAR-T cells engage with tumor cells via the targeted antigen and is characterized by a constellation of symptoms (subject can have one or more symptoms with fever being the sine qua non) including fever, chills, hypotension, hypoxia and in severe cases organ damage e.g. renal failure, coagulopathy, and death. Management of CRS includes targeting IL-6 (thought to be central to CRS pathophysiology) with an IL-6 antibody (tocilizumab), corticosteroids (general suppression of inflammation) and supportive care, such as fluids, vasopressors, oxygen, and ventilatory support etc.

CAR-T cell associated NT, currently referred to as immune effector cell associated neurotoxicity syndrome (ICANS), may manifest as delirium, encephalopathy, aphasia, tremor, seizures, and cerebral edema. NT is thought to be distinct in pathophysiology from CRS and occurs commonly with or after CRS. Symptoms such as headache are thought to be less specific for NT and are not included in current ICANS grading as are more specific but non-life-threatening symptoms like tremor. Corticosteroids and antiseizure medications (prophylaxis or treatment) form the cornerstone of NT management. Tocilizumab or other IL6 blocking agents are given in NT if subjects have concurrent CRS; use in NT alone has raised concern for worsening NT due to higher levels of IL-6 in the CSF.[9, 10]

Given risk of life threatening and fatal toxicities with CRS and NT, all commercially available CAR-T cell products have a black box warning for these toxicities and are available only with a restricted program called Risk Evaluation and Mitigation Strategy (REMS) in place. Finally, there is a theoretical risk of secondary malignancy resulting from insertional mutagenesis in products modified with retroviral vectors. When gene therapies were first being developed, hematopoietic stem cells (HSCs) which had undergone retroviral transduction were transplanted into subjects with chronic granulomatous disease or severe combined immunodeficiency. T cell leukemias originating from insertional mutagenesis events were diagnosed in recipients of those therapies up to 15 years after infusion of the modified HSCs. Today's retrovirally transduced CAR T cell

products are designed to proliferate following administration, and in some cases, they may persist in the body for several years. As such, the theoretical possibility of insertional oncogenesis remains.

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

- Lisocabtagene maraleucel has been FDA approved since February 5, 2021, for treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), PMBCL, HGBL, and DLBCL arising from indolent lymphoma and follicular lymphoma 3B (FL3B).
- Lisocabtagene maraleucel has also been approved by the European Union and Japan since 2021.
- The benefit/risk profile of lisocabtagene maraleucel has not changed since its initial approval.
- This is the first supplement to be submitted for additional new indications.

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

- Study BCM-003 and Study 17001 were conducted under IND 16506.
- 27 April 2016: orphan drug designation (ODD) granted to lisocabtagene maraleucel for the treatment of DLBCL (designation 15-5161).
- 15 December 2016: breakthrough therapy designation (BTD) granted to lisocabtagene maraleucel for the treatment of patients with relapsed/refractory aggressive large B-cell NHL, including DLBCL NOS, de novo or transformed from indolent lymphoma, PMBCL or grade 3B follicular lymphoma.
- 20 October 2017: regenerative medicine advanced therapy (RMAT) designation granted to lisocabtagene maraleucel for the treatment of patients with relapsed/refractory aggressive large B-cell NHL, including DLBCL NOS, de novo or transformed from indolent lymphoma, PMBCL or grade 3B follicular lymphoma.
- 12 July 2018: Orphan drug designation (ODD) for treatment of PMBCL granted (#DRU-2018-6440)
- 05 February 2021: lisocabtagene maraleucel received regular approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, 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 (BLA 125714/0).
- 02 July 2021: Type B Written Response Only meeting was granted to obtain Agency comments on proposed methodology to set indication-associated specifications for LBCL, second-line patients.
- 22 October 2021: Type B Teleconference Pre-sBLA Meeting was held with the Agency with key issues discussed: i) incorporation of clinical findings of progression in the final adjudication of response by the IRC oncologist, ii) FDA reiterated their request to include an Integrated Summary of Safety (ISS) in the

sBLA.

- 23 December 2021: supplemental BLA 125714/90 submitted for second-line therapy.

2.6 Other Relevant Background Information: Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of the clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

All studies conducted in the lisocabtagene maraleucel development program were reported to meet International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. For studies conducted under the IND, investigators were required to ensure adherence to the basic principles of GCP. No critical audit findings were reported.

Three Bioresearch Monitoring (BIMO) inspection assignments were issued for this BLA, and these were completed and classified as No Action Indicated (NAI). BCM-003 is a global study conducted in 11 countries and 53 sites. At the closeout meeting, no FDA 483, Inspectional Observations was issued

There was no clinical study conduct or data integrity issues that impacted the clinical review of this submission. The studies supporting this submission appear to have been conducted in compliance with good clinical practices that included obtaining informed consent, and in accordance with acceptable ethical standards.

3.3 Financial Disclosures

Disclosable financial interests were reported in the small minority of investigators and do not affect the overall study results. Please see details in Appendix 2.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Lisocabtagene maraleucel is a CD19 directed, genetically modified, autologous T cell immunotherapy product that consists of 1:1 CD4 and CD8 T cell components that are infused separately but sequentially (minutes apart). To prepare lisocabtagene maraleucel, a subject's own T cells are harvested (via standard leukapheresis) and the purified CD4+ and CD8+ T cells are separately activated and transduced ex-vivo with a replication incompetent vector to express a CAR comprising an anti-CD19 monoclonal antibody-derived single-chain variable fragment (scFv), immunoglobulin (IgG) 4 hinge region, CD28 transmembrane domain, 4-1BB costimulatory domain and a CD3 zeta activation domain. CD3 zeta signaling is critical for initiating T-cell activation and anti-tumor activity, while 4-1BB signaling is responsible for enhanced expansion and persistence of lisocabtagene maraleucel. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved separately.

Lisocabtagene maraleucel formulation contains 75% volume by volume (v/v) Cryostor® CS10 which contains 7.5% dimethylsulfoxide (v/v), 24% (v/v) Multiple Electrolytes for Injection, Type 1, and 1% (v/v) of 25% human albumin. The product must pass a sterility test before release for shipping as a frozen suspension in subject-specific vials. The product is then thawed and infused back into the subject where anti-CD19 viable CAR-T cells can recognize and eliminate CD19 antigen positive tumor cells.

4.2 Assay Validation

Please refer to the original BLA application 125714/0 for details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the original BLA application 125714/0 for details.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology Review Memo for details and the review of the original BLA application 125714/0.

- **4.4.1 Mechanism of Action**

The mechanism of action of lisocabtagene maraleucel in R/R LBCL is consistent with the known mechanism of action of anti-CD19 chimeric antigen receptor (CAR)-T cell therapy. CAR-T cells mediate major histocompatibility complex (MHC)-unrestricted tumor cell killing by enabling T cells to bind target cell surface antigens through a single-chain variable fragment (scFv) recognition domain.

- **4.4.2 Human Pharmacodynamics (PD)**

B-cell aplasia, defined as < 3% of CD19+ B cells in peripheral blood lymphocyte, is on target off tumor pharmacodynamic effect of lisocabtagene maraleucel. In Studies BCM-003 and 017006, B-cell aplasia was observed in 95-100% of subjects at 2-3 months following lisocabtagene maraleucel treatment. In Study 017006, an increase in the proportion of subjects with B-cell aplasia was observed from 80% (46 of 60) of subjects at baseline to 100% (53 of 53) of subjects at Day 29, with continued B-cell aplasia at 95.2%

(40 of 42) through Day 90.

- **4.4.3 Human Pharmacokinetics (PK)**

Pharmacokinetic parameters such as maximum observed blood concentration (Cmax), time of maximum observed blood concentration (Tmax), and area under the blood concentration-time curve from time zero to 28 days after dosing (AUC[0-28]), based on polymerase chain reaction (PCR) to detect lisocabtagene maraleucel transgene vector sequences in blood samples for subjects in 2L LBCL, were similar to those for subjects in 3L+ LBCL in Study 017006. In Study BCM-003, the PK analysis indicate comparability of Cmax, Tmax and AUC between subjects who crossed over from standard therapy and the lisocabtagene maraleucel arm. The median Tmax occurred 10 days after infusion in treated subjects with 2L LBCL. Persistence of liso-cel transgene was observed in 35% of subjects at the Month 11 post lisocabtagene maraleucel infusion visit in Study BCM-003 and 33% of subjects at Month 18 in Study 017006.

4.5 Statistical

Studies BCM-003 and 017006, met the pre-specified efficacy criteria. The statistical analysis results provide sufficient evidence to support the recommended second-line indications for lisocabtagene maraleucel. FDA's statistical reviewer verified that the key endpoint analyses reported by the Applicant were supported by the submitted datasets. In Study BCM-003, starting a new antineoplastic therapy due to efficacy concerns could bias the EFS endpoint in an open-label trial as investigators might put more standard therapy subjects into a new therapy intentionally or unintentionally. However, since the observed number of subjects who met this EFS component is very similar between the two arms, it was not necessary to conduct further analysis on the primary efficacy endpoint.

4.6 Pharmacovigilance

Because of the risk of CRS and neurologic toxicities, lisocabtagene maraleucel was originally approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). With the REMS, hospitals and their associated clinics that dispense lisocabtagene maraleucel must be specially certified, and health care providers involved in the prescribing, dispensing, or administering of lisocabtagene maraleucel must be trained to recognize and manage CRS and nervous system toxicities. Refer to the original BLA application 125714/0 for details.

The pharmacovigilance plan includes a long-term, observational registry study for patients treated with lisocabtagene maraleucel. This postmarketing requirement (PMR) study will follow the recipients of lisocabtagene maraleucel for 15 years to characterize the incidence and severity of selected adverse events (AEs), including secondary malignancy. Secondary malignancies must be reported by treating physicians to the Applicant within 72 hours of diagnosis to expedite AE reporting and to initiate a separate, non-protocol-related process for tumor specimen processing, and testing for lisocabtagene maraleucel vector sequence for secondary malignancies of T cell origin.

Reviewer comment(s)

The REMS with ETASU and the PMR safety study are the recommendation of the clinical review team with concurrence from the pharmacovigilance reviewers from the Center for Biologics Evaluation and Research (CBER) Office of Biostatistics and Pharmacovigilance (OBPV), Center for Drug Evaluation and Research (CDER) Division of Risk Management

(DRISK), and the CBER Safety Working Group. The goal of the REMS is to ensure that sites are prepared for the safety risks of lisocabtagene maraleucel that were identified in the IND phase of product development. The PMR registry study addresses the theoretical concerns of insertional mutagenesis and/or the development of lisocabtagene maraleucel related secondary malignancy. The Applicant is proposing to enroll approximately 1700 patients (500 from clinical trials) including at least 200 patients treated with lisocabtagene maraleucel as second-line therapy and follow each patient for up to 15 years. However, in absence of new safety signal, the clinical team in consultation with OBPV agreed to limit the number of patients to 1500.

The clinical review team recommends that the label inform of the requirement to monitor patients at the certified healthcare facility daily for at least seven days following infusion of lisocabtagene maraleucel for signs and symptoms of CRS and neurologic events. This recommendation is based on the requirements in the protocol, the clinical data related to the timing of onset of neurologic and CRS events, and the availability of guidance to treat these serious adverse events. The knowledge of and experience with CAR-T cell therapy products has expanded over the intervening years, and with adequate safety procedures in place, outpatient monitoring is considered acceptable after lisocabtagene maraleucel infusion.

Discussions with the Applicant are ongoing regarding the final REMS and ETASU documents. Please refer to the action letter for final wording of the PMR.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical review of this submission was based on the results of the randomized controlled study, BCM-003, and the single-arm study, 017006. Both studies were submitted in Module 5 of this BLA. These studies are described in Section 5.23.

Data reviewed included tabulation and analysis datasets, the clinical study report, the study protocol, the independent review committee charter, the statistical analysis plan, the informed consent document, case report forms (CRFs), multiple information requests (IRs), and data in the public domain. JMP 16 (SAS Institute, Inc.) was used to reproduce analyses based on the submitted datasets and to conduct additional exploratory analyses.

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

See Section 5.1.

5.3 Table of Studies/Clinical Trials

A listing of clinical studies relevant to this sBLA is provided in Table 1. Studies BCM-003 and 017006 are the primary basis for the efficacy and safety review. Subjects treated with lisocabtagene maraleucel on both studies received the same treatment regimen. Surviving subjects in both studies are to be followed for 15 years after lisocabtagene maraleucel infusion. Studies in third line or later (3L+) relapsed/refractory DLBCL are outlined in Table 2. Only Study 017001 was added in the integrated safety summary (ISS).

Table 1: Clinical Studies of Lisocabtagene Maraleucel for Second-Line Therapy.

Study	Study Design	Subject Population	Product, Dosage	No. of Subjects Enrolled, Treated Planned	Study Status
BCM-003	Phase 3, randomized, open-label, parallel-group, multicenter trial	R/R NHL after failure of 1 line of prior therapy; HSCT eligible adults	Single dose JCAR017 (100×10^6 CAR+ T cells) IV	184 (92 to the lisocabtagene maraleucel arm and 92 to the standard therapy arm),	Ongoing; Primary CSR (data cutoff 08 Mar 2021)
017006	Phase 2, open label, single-arm multicenter trial	R/R NHL after failure of 1 line of prior therapy in HSCT-ineligible adults	Single dose JCAR017 (100×10^6 CAR+ T cells) IV	73 enrolled; 61 treated; approximately 62 treated	Ongoing; Interim CSR (data cutoff 28 May 2021)

(Source: Adapted from BLA 125714/90.0, 2.7.6 Synopsis of Individual Studies, Table 1)

Reviewer comment(s)

One hundred and fifty subjects with LBCL received conforming products as second-line therapy and were considered the safety analysis population. An additional two subjects,

albeit treated, received non-conforming product.

The R/R aggressive NHL population included subjects with DLBCL NOS, HGBL, PMBCL, and FL grade 3B.

Table 2: Studies Conducted with Lisocabtagene Maraleucel: 3L+ and LTFU.

Study	Primary Objective	Study Design	Dose Regimen	No. of Subjects Treated	Population	Study Status
017001	- Safety -Antitumor activity (ORR)	Phase 1, open-label, single-arm, multi-cohort multicenter trial	DL1: 50×10^6 CAR+ T cells DL2:100×10^6 CAR+ T cells DL3:150×10^6 CAR+ T cells	268 DLBCL, 17 MCL.	R/R CD19+ B-NHL DLBCL: ≥2 prior therapies, or MCL: ≥1 prior therapy	Ongoing; - MCL cohort - FL3B in DLBCL cohort - Follow-up for all subjects through 2 yrs post-treatment
JCAR 017-BCM-001	-Efficacy: (ORR) Cohort 1, 2 - Safety: Cohort 7	Phase 2, open-label, single-arm, multicohort multicenter trial	JCAR017; 100×10^6 CAR+ T cells	71 enrolled. Cohort 1: 36 treated. 34 planned Cohort 2:18 treated. 28 planned	R/R CD19+ B-NHL. ≥ 2 prior therapies (Cohort 1,7) 1 prior therapy (Cohort 2)	Ongoing; Safety data included in the ISS and SCS (data cutoff 04-Jan-2021)
017007	Safety in the nontertiary care setting	Phase 2, open-label, single-arm, multicenter trial	JCAR017; 100×10^6 CAR+ T cells	94 enrolled. 71 treated. 80 planned	R/R CD19+ B-NHL; ≥ 2 prior therapies	Ongoing; Safety data included in the ISS and SCS (data cutoff 02 Mar 2021)
GC-LTFU-001	Long Term safety Long-term efficacy	Long-term safety follow-up	NA	93 treated	All subjects (adult and pediatric	Ongoing; Safety data included in the ISS and SCS (data cutoff 08 Mar 2021)

ISS = integrated summary of safety; LTFU = long-term follow-up; MCL = mantle cell lymphoma; SCS = summary of clinical safety
(Source: Adapted from BLA 125714/90.0, 2.7.6 Synopsis of Individual Studies, Table 1)

Reviewer comment(s)

We included Study 017001 in a pooled safety analysis, because it provided safety data from an additional 268 subjects, leading to a total of 418 subjects with LBCL treated with lisocabtagene maraleucel to inform the safety of the product.

5.4 Consultations

No consultation was requested for this study.

- **5.4.1 Advisory Committee Meeting**

The application was not presented to an Advisory Committee as it did not raise significant efficacy concerns or any new safety signals.

- **5.4.2 External Consults/Collaborations**

The application was not presented to external consultants.

5.5 Literature Reviewed

1. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K *et al.* Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol* 2016; **174**(1)**:** 43-56. e-pub ahead of print 2016/05/20; doi: 10.1111/bjh.14136

2. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. *Blood Rev* 2017; **31**(2)**:** 37-42. e-pub ahead of print 2016/10/09; doi: 10.1016/j.blre.2016.09.004

3. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA: a cancer journal for clinicians* 2010; **60**(6)**:** 393-408. e-pub ahead of print 2010/10/30; doi: 10.3322/caac.20087

4. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program* 2011; **2011:** 498-505. e-pub ahead of print 2011/12/14; doi: 10.1182/asheducation-2011.1.498

5. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D *et al.* Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995; **333**(23)**:** 1540-1545. e-pub ahead of print 1995/12/07; doi: 10.1056/nejm199512073332305

6. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M *et al.* Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010; **28**(27)**:** 4184-4190. e-pub ahead of print 2010/07/28; doi: 10.1200/jco.2010.28.1618

7. Farooq U, Maurer MJ, Thompson CA, Thanarajasingam G, Inwards DJ, Micallef I et al. Clinical heterogeneity of diffuse large B cell lymphoma following failure of front-line immunochemotherapy. Br J Haematol 2017; 179(1): 50-60. e-pub ahead of print 2017/06/28; doi: 10.1111/bjh.14813

8. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017; 130(16): 1800-1808. e-pub ahead of print 2017/08/05; doi: 10.1182/blood-2017-03-769620

9. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014; 124(2): 188-195. e-pub ahead of print 2014/05/31; doi: blood-2014-05-552729 [pii] 10.1182/blood-2014-05-552729 [doi]

10. Santomasso B, Bachier C, Westin J, Rezvani K, Shpall EJ. The Other Side of CAR T-Cell Therapy: Cytokine Release Syndrome, Neurologic Toxicity, and Financial Burden. Am Soc Clin Oncol Educ Book 2019; 39: 433-444. e-pub ahead of print 2019/05/18; doi: 10.1200/edbk_238691

11. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E *et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**(27)**:** 3059-3068. e-pub ahead of print 2014/08/13; doi: 10.1200/jco.2013.54.8800

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1. Study BCM-003 (TRANSFORM)

Study identification codes

- IND # 016506
- EudraCT number 2018-000929-32
- ClinicalTrials.gov identifier NCT03575351

Study Title: A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects with High-Risk, Transplant-Eligible Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphomas.

• 6.1.1 Objectives

Primary objective:

- Compare EFS in subjects treated with lisocabtagene maraleucel versus standard therapy.
- Describe the rate of completion of high-dose chemotherapy (HDCT) and HSCT.

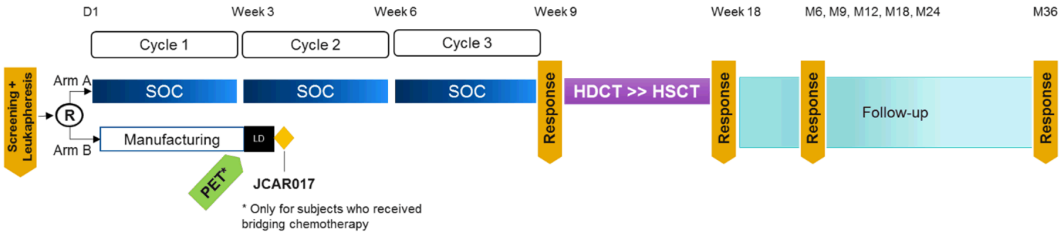
Secondary objectives:

- Compare the efficacy in subjects treated with lisocabtagene maraleucel versus subjects treated according to standard therapy defined as complete rate response (CRR), progression-free survival (PFS), and overall survival (OS).
- Compare other parameters of efficacy, defined as duration of response (DOR) overall response rate (ORR), PFS on next line of treatment (PFS-2).
- Compare efficacy rates (EFS, PFS, OS) at 6, 12, 24 and 36 months after randomization.
- Compare the safety defined as type and frequency of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities.
- Compare the safety and efficacy in clinical, histological, and molecular subgroups.
- Assess HRQoL and health economics and outcomes research.

• 6.1.2 Design Overview

Study BCM-003 is a randomized, open-label, parallel-group, multicenter, Phase 3 study to demonstrate the efficacy and safety of lisocabtagene maraleucel versus standard salvage therapies in subjects with aggressive B-cell NHL who are refractory to front-line immunochemotherapy or have relapsed within 12 months and are eligible for HDCT and autologous HSCT. The study opened on October 23, 2018, with data cutoff for this sBLA on March 08, 2021. The time of relapse was calculated from the date of the first disease assessment confirming a complete response (CR) obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse. Figure 1 depicts the Study Design.

Figure 1: Study Design (BCM-003).



Abbreviations: JCAR017 = liso-cel; LD = lymphodepleting; R = randomization; SOC = standard therapy. (Source: Protocol Figure 1)

The study consisted of four periods:

1) Screening: Study Days -28 to-1.

2) Treatment Period: (Study Days 1 ± 3 days to 126 ± 7 days) consisted of randomization to either Arm A (standard therapy followed by HDCT and HSCT) or Arm B (bridging therapy if needed, LDC followed by lisocabtagene maraleucel infusion Day 29 ± 7 days (2 days to 7 days after completion of LDC). The first response evaluations were performed at week 9 (after three cycles of SOC for Arm A and 5 weeks after lisocabtagene maraleucel for Arm B) and Week 18 (8 weeks after the start of HDCT for Arm A and 14 weeks after lisocabtagene maraleucel infusion for Arm B).

3) Post Treatment Period: Consisted of further efficacy and safety follow-up visits at Months 6 (± 10 days), 9, 12, 18, 24, and 36 (± 14 days) (end of study [EOS]) or early termination (ET).

4) Survival Follow-up

- **6.1.3 Population**

Key inclusion criteria included

As per protocol amendment 2:

- Aged ≥ 18 years and ≤ 75 years old
- Histologically proven DLBCL NOS (de novo or transformed indolent NHL), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (DHL/THL), PMBCL, THRBCL or FL3B. (Note: Subjects with secondary CNS involvement were eligible).
- Refractory disease (SD, PD, PR or CR with relapse before 3 months) or relapsed disease (defined as CR lasting at least 3 months but no more than 12 months), to CD20 antibody and anthracycline containing first-line therapy for disease under study (Note: The time of relapse was calculated from the date of the first disease assessment confirming a CR obtained with first-line treatment for disease under study, to the date of first assessment demonstrating a relapse).
- Active or uncleared Hepatitis B, hepatitis C or HIV at time of screening.
- PET positive lesion per Lugano criteria (Deauville score 4 or 5).
- Adequate organ function:
  - Absolute neutrophil count ≥ 1.0×10^9 cells/L and platelets ≥ 50×10^9 cells/L in absence of bone marrow involvement.
  - Cockcroft Gault creatinine clearance > 45 ml/min.

  - Alanine aminotransferase (ALT) ≤ 5 x ULN.
  - Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver.
  - By echocardiogram, left ventricular ejection fraction ≥ 40% or by MUGA within 4 weeks of randomization.
  - Oxygen saturation ≥ 92% on room air and FEV1 ≥ 50%.
- ECOG performance status (PS) of 0 or 1.

Key exclusion criteria included:

- Not eligible for autologous HSCT or planned to undergo allogeneic HSCT
- Primary cutaneous large B-cell lymphoma, EBV (Epstein-Barr virus) positive DLBCL, Burkitt lymphoma or transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter transformation.
- History of another primary malignancy that had not been in remission for at least 2 years.
- Prior gene therapy product or prior CD19- target therapy.
- Uncontrolled systemic infections.
- Clinically significant cardiovascular conditions within 6 months prior to sign the informed consent form (ICF).
- Venous thrombosis or embolism not managed on a stable regimen of anticoagulation.

Reviewer comment(s)

- *BCM-003 enrolled population that was eligible for autologous HSCT. By week 5 evaluation in the lisocabtagene maraleucel arm, subjects would have received the CAR-T therapy allowing for the first post-treatment response assessment. In the standard therapy arm, this assessment was done by week 9 to capture responses to three cycles of salvage chemotherapy upon which the decision to proceed with HSCT was taken.*
- *Assessment by week 18 (Day 126) from randomization was done to capture the response of the control arm after completion of HDCT and HSCT.*
- *The long-term follow-up (LTFU) in the lisocabtagene maraleucel arm is 15 years, there were no LTFU planned for the standard therapy arm since long term toxicities of the regimens are known.*

- **6.1.4 Study Treatments or Agents Mandated by the Protocol**

Following screening, leukapheresis was performed on each subject to collect enough peripheral blood mononuclear cells to produce lisocabtagene maraleucel prior to randomization, irrespective of treatment arm. The following treatments were administered:

- Subjects randomized to Arm A received standard therapy followed by HDCT and autologous HSCT.
- Subjects randomized to Arm B received bridging therapy, if needed followed by LDC and lisocabtagene maraleucel.

Arm A – Standard of Care Reference Therapies

Subjects randomized to Arm A were administered one of the following three standard therapy regimens, as per the investigator's decision, followed by HDCT and autologous

HSCT:

1. R-DHAP: Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, cytarabine 2 x 2000 mg/m² on Day 2, and cisplatin 100 mg/m² on Day 1.
2. R-ICE: Rituximab 375 mg/m² on Day 1, ifosfamide 5000 mg/m² on Day 2, etoposide 100 mg/m² on Days 1 to 3, carboplatin area under the curve (AUC) 5 (maximum dose 800 mg) on Day 2; or
3. R-GDP: Rituximab 375 mg/m² on Day 1, dexamethasone 40 mg on Days 1 to 4, gemcitabine 1000 mg/m² on Days 1 and 8, cisplatin 75 mg/m² Day 1.

All subjects randomized to Arm A received three cycles of standard therapy salvage therapy (R-DHAP, R-ICE, or R-GDP, as above) as per physician's choice, during which peripheral blood hematopoietic stem cells for HSCT were harvested. After three cycles, response was evaluated by PET-CT. Subjects responding to standard therapy (CR and PR) were to proceed to HDCT and autologous HSCT.

The study allowed subjects randomized to Arm A to crossover from Arm A to Arm B if requested by investigator and upon central confirmation of the following: failure to achieve CR or PR by week 9 post randomization (after three cycles of standard therapy); progression at any time, need to start a new antineoplastic therapy due to efficacy concerns after 18 weeks post randomization.

Reviewer comment(s)

Of the 92 subjects randomized to Arm B, 50 (54%) subjects were approved to crossover by medical monitor after IRC confirmation of a qualifying event and 47 subjects received lisocabtagene maraleucel. The most common reason for crossing over was progression in 30 (72%) of the subjects, followed by suboptimal response in 8 (16%) subjects and relapse in 6 (12%) subjects. The median time from randomization to approval of crossover was 2.5 months (range 1 to 10 months) [IQ 2, 3].

Arm B – lisocabtagene maraleucel

Subjects completed the assessments prior to start LD. Bridging therapy was allowed in this trial for subjects with bulky disease, or manufacturing delay and a PET was done prior to proceed to LD.

Lymphodepleting Chemotherapy: LDC start was to start 5 to 7 days before lisocabtagene maraleucel infusion and was to be completed 2 days before lisocabtagene maraleucel infusion, administer:

- 0.9% sodium chloride (NaCl) given at 500 mL/hr., starting 2 hours prior to cyclophosphamide.
- Fludarabine IV 30 mg/m^2 over 30 minutes (dose adjusted for CrCl) per day for 3 days.
- Cyclophosphamide IV 300 mg/m^2 over 60 minutes per day for 3 days.
- Additional 1 L of 0.9% NaCl given at 500 mL/hr.

Lisocabtagene maraleucel:

- Acetaminophen 500 to 650 mg by mouth (PO) and
- Diphenhydramine 25 to 50 mg PO 30-60 minutes prior to administration and could be repeated every 6 hours per the investigator's assessment.
- Lisocabtagene maraleucel was infused at a dose of 100 × 10^6 CAR+ viable T cells

(CAR+ T cells) on Day 29 (2 to 7 days after completion of LDC).

Reviewer comment(s)

98% of subjects in the lisocabtagene maraleucel arm received a median lisocabtagene maraleucel dose of 99.92 × 10^6 CAR+ viable T cells. All doses were within the pre-specified acceptable dose range, and the observed degree of deviations from the target is unlikely to have significantly altered the primary study outcomes.

Bridging Chemotherapy

Bridging chemotherapy with one of the protocol-defined standard therapy regimens was allowed for disease control if deemed appropriate by the investigator and between the leukapheresis and up to 7 prior LDC.

Reviewer comment(s)

Of the 89 subjects who were treated with lisocabtagene maraleucel, 58 (65%) subjects were given bridging therapy consisting in one of the following standard therapy regimens:

- *R-ICE 29 subjects (33%)*
- *R-GDP 16 subjects (18%)*
- *R-DHAP 13 subjects (15%)*

PET positive disease was not required for eligibility post bridging therapy, eight subjects were PET negative after bridging as per investigator assessment. A key aspect of the protocol that ensured that the EFS assessment was not confounded by the effects of bridging include the blinded IRC assessment of EFS for both arms.

- **6.1.5 Directions for Use**

- The Applicant ensured appropriate monitoring procedures were performed before, during and after the study. The following is the schedule of events during the study including monitoring throughout the study and post treatment.
- Lisocabtagene maraleucel was supplied cryopreserved in subject specific vials and thawed prior to administration. The CD8 and CD4 components were thawed and administered separately by IV infusion, with the CD8 component administered first, followed by the CD4 component. Instruction regarding storage and administration are detailed in the approved label.

- **6.1.6 Sites and Centers**

A total of 47 clinical sites in 11 countries participated in BCM-003 trial. Thirty in the United States, twenty-one in Europe and four sites in Japan participated in the trial.

- **6.1.7 Monitoring and Surveillance**

Subjects were evaluated during visits that took place over four periods: 1) Screening (eligibility and leukapheresis), 2) treatment (standard therapy or bridging therapy [if needed], LDC, and lisocabtagene maraleucel), 3) post-treatment, and 4) Survival Follow-up.

1. **Screening Period**

Screening evaluations were performed in all subjects to determine study eligibility and the following was completed within 4 weeks prior to randomization.

- Subject were registered in the interactive response technology (IRT) system.
- Obtained medical history and physical and neurologic examination, sAAIPI status, and ECOG PS assessment.
- HCT-CI (hematopoietic cell transplantation – specific comorbidity index).
- Laboratory evaluations included: hematology, chemistry, coagulation, pregnancy tests, inflammatory markers, Ig, viral serology, creatinine clearance, urinalysis.
- Research samples included: plasma samples, peripheral blood mononuclear cells (PBMCs), detection of B-cell aplasia.
- CSF assessment and brain MRI if CNS involvement suspected.
- Positron emission tomography (PET) and computed tomography (CT) /MRI scan to confirm the presence of PET-positive lymphoma.
- Tumor biopsy collected for central confirmation of diagnosis.
- Recorded all AEs concomitant medications and concomitant procedures related to protocol mandated procedures, and radiation therapy.
- An unstimulated leukapheresis collection was performed on each subject to obtain enough PBMCs for the production of the lisocabtagene maraleucel irrespective of the arm assigned.

The following assessments were performed on the day of leukapheresis:

- Eligibility check, evaluation for active infections, ECOG PS, vital signs.
- Blood samples for hematology and chemistry panel.
- Recorded AEs, concomitant medications, and procedures.

2. Treatment period

Day 1 - Randomization (+ 3 days), Days 8 and 15 (± 2 days)

Subjects were randomized to either Arm A or Arm B per the IRT system.

The following assessments were performed after randomization and prior to treatment:

- Confirmation of eligibility, ECOG PS, physical, neurologic examination, MMSE.
- Laboratory evaluations included: Hematology, chemistry, coagulation tests, and inflammatory markers.
- Record all AEs, concomitant medications, and concomitant procedures
- Quality of life questionnaires.
- Stem cell collection was performed before Day 71.

Subjects in Arm A who discontinued treatment were scheduled for early termination (ET) visits and subsequently followed on Days 29, 36, 50, 64, 71, 85, 99 and 126.

Days 22 (± 7 days)

Arm A (standard therapy): The following assessments were performed:

- Laboratory evaluations as described on the screening period.
- Subjects received second cycle of standard therapy and registered in the IRT system.

Arm B (lisocabtagene maraleucel): LD chemotherapy was initiated and completed 2 to 7 days prior to lisocabtagene maraleucel infusion. Subjects who received bridging chemotherapy had a PET prior to LD. Brain MRI and CFS assessment were performed if there was a secondary CNS involvement.

The following assessments were performed on each day before LD:

- Adequate organ function and no evidence of active infections.
- Complete physical examination, weight, vital signs, ECOG PS.
- Laboratory tests included: hematology and chemistry panel, coagulation tests, inflammatory markers, creatinine clearance, pregnancy test.
- PET only for subjects receiving bridging chemotherapy
- Recorded all AEs, concomitant medications, and procedures

Day 29 (± 7 days)

Arm A: The assessments performed on Day 29 were similar to those done on Day 1

Arm B: The following assessments were performed prior to the lisocabtagene maraleucel infusion:

- Confirmation of eligibility criteria. Any of the following criteria delayed the administration of lisocabtagene maraleucel:
  - Suspected or active systemic infection
  - Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
  - Chest x-ray abnormalities or O2 requirement to keep saturation above 91%
  - Uncontrolled cardiac arrhythmia or hypotension requiring vasopressor support
  - Organ dysfunction ≥ Grade 3
  - Taking any of the prohibited medications
  - Progressive vascular tumor invasion, thrombosis, or embolism
- ECOG PS, vital signs, physical and neurologic examination, MMSE
- Laboratory evaluations including hematology, chemistry, coagulation, immunoglobulin tests, inflammatory markers, detection of B-cell aplasia, urinalysis.
- Research samples: plasma samples, PBMCs.
- Recorded all AEs, concomitant medications including new anti-lymphoma therapy (NALT) and procedures.
- Quality of life questionnaires
- Subjects received their lisocabtagene maraleucel infusion and registered in IRT system.

Day 31 (±1 day), Day 39 (± 1 day), Day 43 (± 6 days) and Day 50 (± 2 days)

The assessments performed on Day 31, Day 39, Day 43, and Day 50 were the same as the assessments performed on Day 29.

Arm A: Subjects received third cycle of standard therapy (Day 43), registered in IRT system.

Arm B: All visits for Arm B subjects were scheduled based on Day 29 lisocabtagene maraleucel infusion.

64 (± 6 days) and Day 71 (± 6 days)

- ECOG PS, physical and routine neurologic examination.
- Response assessments: PET and CT/MRI.

Arm A: Assessments performed prior to receiving HDCT for Arm A including:

- ECOG PS, physical exam, vital signs
- Laboratory evaluations including hematology and chemistry panel, coagulation tests, chemistry panel, inflammatory markers, Urinalysis
- Subjects underwent HDCT prior to receiving the HSCT upon confirmation they meet eligibility to undergo HDCT and HSCT. Any of the following criteria delayed the HSCT had HDCT:
    - Active systemic infection
    - Fever ≥ 38°C/100.4°F, not related to underlying disease
    - CXR abnormalities or requirement for O2 to keep saturation above 91%
    - Cardiac arrhythmia, and/or hypotension requiring vasopressors
    - Organ dysfunction ≥ Grade 3.
    - Taking any of the prohibited medications.

Arm B:

- Immunogenicity (serum and PBMCs).
- Record all AEs, concomitant medications, and procedures.

Day 85 (± 6 days), Day 99 (± 7 days), Day 106 (± 7 days), Day 126 (± 7 days)

For Arm A subjects, this visit was scheduled based on date of the HDCT (Day 71).

The assessments performed were the same as Day 64.

- Response assessments: PET and CT/MRI (Week 18).

3. Post-Treatment Period

Follow-up: Months 6 ((±10 days), 9, 12, 18, 24, and 36 (± 14 days)

All randomized subjects who received study treatment, including subjects who withdraw from treatment and those with progressive disease had post-treatment follow-up visits at Months 6, 9, 12, 18, 24 and 36 (or end of study [EOS]).

- ECOG PS, physical examination, vital signs, pregnancy test (Month 9, 12 [Arm B] and Month 36 [Arm A and B])
- Laboratory, research samples: hematology and chemistry panel, immunoglobulins, RCL testing (Months 12, 18, 24, 36) (Arm B), immunogenicity (serum and PBMCs at Month 36) (Arm B).
- B-cell aplasia (Months 12, 18, 24, 36) (Arm B).
- Response assessments: PET and CT/MRI.
- Recorded AEs, concomitant medications, NALT and procedures.
- Quality of life questionnaires and hospital resource utilization assessment
- The EOS visit was registered in IRT system (Month 36).

4. Survival Follow -up:

After the EOS visit, all subjects will be followed for survival monthly. Because this

protocol involves gene transfer, long-term follow-up for lentiviral vector safety, disease status, and survival will continue after EOS under a separate LTFU protocol thereafter for up to 15 years after the lisocabtagene maraleucel infusion.

- **6.1.8 Endpoints and Criteria for Study Success**

Primary endpoint:

- EFS by IRC, defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first.
    - Failure to achieve CR or PR was evaluated after three cycles of standard therapy for Arm A (expected 9 weeks post-randomization) and 5 weeks after the lisocabtagene maraleucel infusion for Arm B.

Key secondary endpoints:

- Complete response rate (CRR), defined as the proportion of subjects achieving a CR from randomization up to 3 years post-randomization. Subjects with unknown or missing response will be counted as non-responders in the analysis. Any responses after a start of a new antineoplastic therapy will not be considered. Responses after crossover will be analyzed descriptively.
- Progression-free survival (PFS), defined as the time from randomization to PD or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from randomization to death due to any cause

Additional secondary endpoints include:

- Overall response rate (ORR)
- Duration of response (DOR)
- Safety
- Health-related quality of life
- Hospital resource utilization
- Rate of HDCT completion, rate of HSCT completion, and response rate post-HSCT

- **6.1.9 Statistical Considerations & Statistical Analysis Plan**

BCM-003 is a global randomized multicenter phase 3 trial evaluating the efficacy and safety of lisocabtagene maraleucel versus standard therapy in adults with high-risk, second-line, transplant-eligible relapse/refractory aggressive LBCL with a primary EFS endpoint.

Randomization (1:1) was stratified by response to first-line therapy and secondary age-adjusted International Prognostic Index (sAAIPI). Date of randomization was defined as Day 1. The key secondary endpoints were to be tested hierarchically (CRR, PFS and OS).

The clinical cutoff dates were determined based on the occurrence of the required number of events for the purpose of the interim analysis for efficacy. The time-to-event data herein are interim data. Please refer to Statistical review for detailed information.

Reviewer comment(s):

- *The analysis of EFS (performed at 82% information level) and the key secondary endpoints (PFS, CR rate, and OS) are pre-specified interim analyses, with the significance threshold for each being a one-sided p-value of 0.012 due to the interim look. The corresponding 97.6% CI is wider than the conventional 95% CI presented in this memo and in the prescribing information and is available in the statistical review memo.*
- *OS analyses: The Applicant projects the OS primary analysis to be available by Q4 2022. In addition, a prespecified, descriptive final efficacy analysis will be performed after the last subject randomized has either reached an event or been followed for 3 years after randomization. The final analysis data cut is projected to be in December 2023, since last subject was randomized in December 2020, with results projected to be available in Q2-Q3 2024 (source: response to 6/22/22 IR).*

- **6.1.10 Study Population and Disposition**

6.1.10.1 Populations Enrolled/Analyzed

Intent-to-Treat Population (ITT): included all patients randomized to treatment. All patients in the ITT population were analyzed according to the treatment arm to which they were randomized. The ITT analysis set was the primary population used for the efficacy analysis and the safety analysis set was the primary population for the safety analysis.

Per-Protocol Population (PP): included all randomized patients who met eligibility criteria and did not have major protocol violation as determined by JUNO therapeutics. All decisions to exclude patients from the PP population were made before clinical database lock. The PP population was used to supplement the analysis of the primary efficacy endpoint using the ITT population. All patients in the PP population were analyzed according to the actual treatment received.

Safety Population: included all enrolled patients who have received at least one dose of any study drug. All patients in the Safety population were analyzed according to the actual treatment received. All safety analyses were performed using the Safety population.

6.1.10.1.1 Demographics

The 184 subjects with LBCL included in the efficacy analysis had a median age of 59 years (range 20–75) and were primarily white, non-Hispanic or Latino individuals treated in the United States. The study included slightly more men than women. Demographic characteristics of Study BCM-003 is displayed in Table 3.

Table 3: Demographics Characteristics of Study BCM-003 Subjects.

Parameter	Lisocabtagene Maraleucel Arm N=92	Standard Arm N=92	All N=184
Age (years)			
Mean (standard deviation)	58 (12.5)	54 (14)	56 (13)
Median (min, max)	63 (20, 74)	58 (26, 75)	59 (20, 75)
Sex, n (%)			
Female	48 (52)	31 (34)	79 (43)
Male	44 (48)	61 (66)	105 (58)
Race, n (%)			
White	54 (59)	55 (60)	109 (59)
Not Collected	22 (24)	25 (27)	47 (26)
Asian	10 (11)	8 (9)	18 (10)
Black- African American	4 (4)	3 (4)	7 (4)
Other	2 (2)	1 (1)	3 (2)
Ethnicity, n (%)			
Not Hispanic- Latino	65 (71)	62 (67)	127 (69)
Not Reported	24 (26)	26 (28)	50 (27)
Hispanic or Latino	3 (3)	3 (3)	6 (3)
Unknown	0 (0)	1 (1)	1 (1)

Source: FDA analysis of ADSL dataset.

Reviewer comment(s)

In general, the demographic characteristics were balanced between the lisocabtagene maraleucel arm and the standard therapy arm and were representative of a 2L high-risk LBCL population. The median age was 59 years which is younger than the median age of LBCL transplant eligible patients (66 years), however the median age of Study BCM-003 population is similar to the median age in the Zuma-7 trial and similar to the median age in trials that have evaluated various chemoimmunotherapy regimens in transplant eligible R/R LBCL. There was a slight female predominance (52%) in the lisocabtagene maraleucel arm, compared to the standard therapy arm where 66% of the subjects were male. The study population include only 31 (17%) subjects who were ≥70 years of age providing limited data in the older adults. There was a higher prevalence of LBCL in the white population compared to African American population, however the study had a disproportionate underrepresentation of the African American population (4%).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline subjects' status and tumor characteristics are detailed in Table 4.

Table 4: Baseline Disease Characteristics in Study BCM-003.

Parameter	Lisocabtagene Maraleucel Arm N=92 n (%)	Standard Arm N=92 n (%)	All N=184 n (%)
NHL Type			
DLBCL	60 (65)	57 (62)	117 (64)
High-Grade B-cell Lymphoma with DLBCL histology	22 (24)	21 (23)	43 (24)
PMBCL	8 (9)	10 (11)	18 (10)
THRBCL	1 (1)	4 (4)	5 (3)
FL3B	1 (1)	0 (0)	1 (1)
Best Response to First Line Therapy			
Partial Response	36 (39)	45 (49)	81 (44)
Complete Response	30 (33)	28 (30)	58 (32)
Progressive Disease	18 (20)	13 (14)	31 (17)
Stable disease	5 (8)	5 (5)	12 (7)
Not Evaluable	1 (1)	1 (1)	2 (1)
Disease Prior Response Status			
Refractory	67 (73)	68 (74)	135 (73)
Relapsed	25 (27)	24 (26)	49 (27)
sAAIPI			
0 or 1	56 (61)	55 (60)	111 (60)
2 or 3	36 (39)	37 (40)	73 (40)
Confirmed CNS disease Involvement			
Yes	1 (1)	3 (3)	4 (2)
No	91 (99)	89 (97)	180 (98)

Source: FDA analysis of ADSL dataset.

Abbreviations: CNS = central nervous system; AAIPI = secondary age-adjusted international prognostic index

Reviewer comment(s)

- *There is underrepresentation of racial and ethnic minorities in this study population.*
- *Overall demographic and baseline disease characteristics for the 184 subjects with LBCL included in the two arms were balanced.*
- *It is noted that 73% of the subjects had primary refractory disease and 27% relapsed within 1 year of the first chemoimmunotherapy. Out of the 58 subjects achieved a CR with first-line therapy, 49 subjects (76%) had relapse within 12 months of initiating first-line therapy. Fourteen (24%) had relapse > 12 months after initiating first-line therapy and within 12 months of completing first-line*

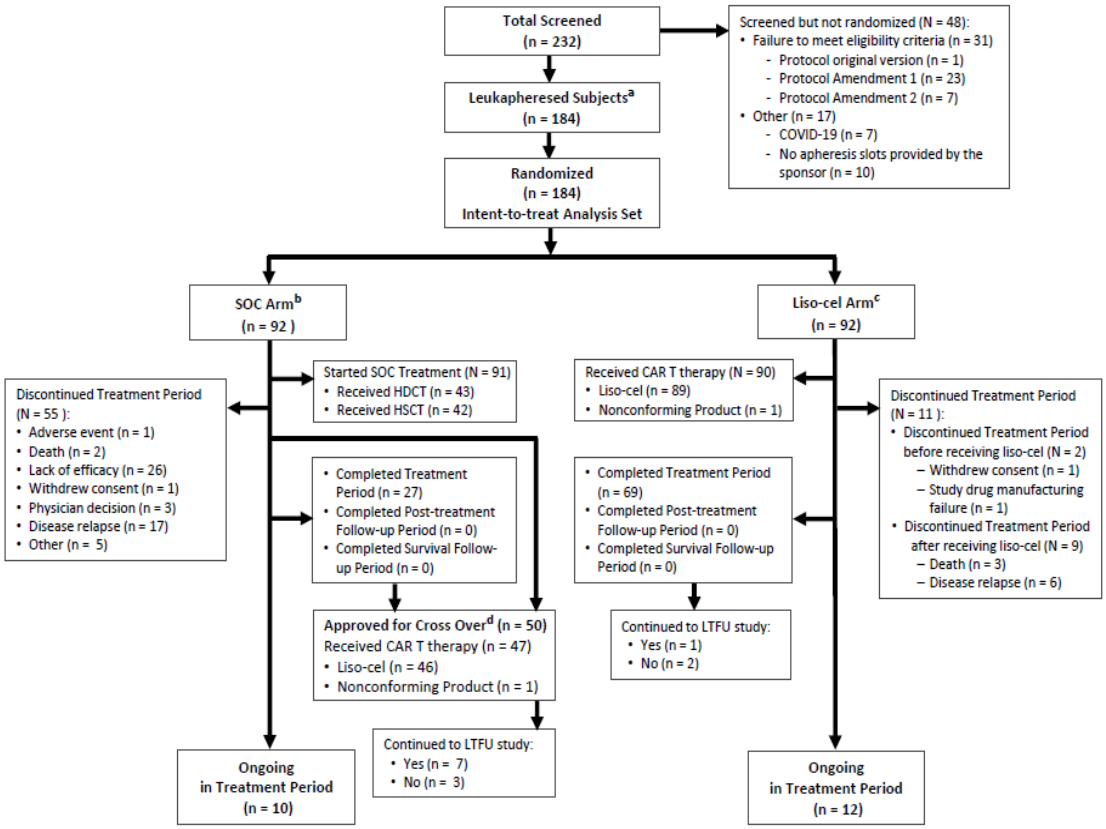
therapy.

- *At the time of the database lock, two subjects had a duration of CR longer than 12 months making both subjects ineligible to participate in Study BCM-003. One subject in the standard therapy arm (subject ID (b) (6)) had a duration of CR of 18.5 months. One subject in the lisocabtagene maraleucel arm (subject ID (b) (6)) had a duration of CR of 12.4 months. Through an IR, the Applicant clarified that for both of these subjects a data entry error was identified in the relapse date after the database lock. Subject (b) (6) had a relapse date on 16-Oct-2019, instead of 16-May-2020 reported at the time of database lock (corrected duration of CR is 11.5 months). Subject (b) (6) had a relapse date on 31-Aug-2020, instead of 14-Sep-2020 reported at the time of database lock (corrected duration of CR is 11.9 months).*

6.1.10.1.3 Subject Disposition

Subject disposition for the study is shown in Figure 2. Patient were randomized (n=92) to standard therapy or (n=92) to lisocabtagene maraleucel arm.

Figure 2: Subject Disposition in Study BCM-003.



[a] *During screening, subjects are assessed for eligibility for randomization and unstimulated leukapheresis.*

[b] *Arm A: Subjects randomized to Arm A were to receive three cycles of standard therapy salvage therapy (rituximab, dexamethasone, cytarabine and cisplatin [R-DHAP], rituximab, ifosfamide, carboplatin and etoposide [R-ICE], or rituximab, gemcitabine, dexamethasone, and cisplatin [R-GDP]) followed by HDCT and HSCT.*

[c] *Arm B: Subjects randomized to Arm B were to receive LDC followed by lisocabtagene maraleucel infusion; bridging therapy was allowed per protocol.*

[d] *Subjects were approved to crossover (from arm A to receive LDC followed by lisocabtagene maraleucel infusion) by the Medical Monitor after IRC confirmation of a qualifying event.*
(Source: BCM-003 Clinical Study Report)

In Study BCM-003, 232 subjects were screened, and 184 were leukapheresed, forty-eight were not randomized. The most common reason was failure to meet eligibility criteria (n=31). An additional 17 (35%) subjects were not randomized; 10 subjects were not randomized because of a contamination at the manufacturing facility and no apheresis slots were available (n=10) and recruitment hold due to COVID-19 (n=7).

Lisocabtagene maraleucel arm

- Out of the 92 subjects randomized to the lisocabtagene maraleucel arm, two subjects did not receive the lisocabtagene maraleucel; one because of manufacturing failure and one subject withdrew consent due to rapid progression of disease.
- Out of the 90 subjects who received lisocabtagene maraleucel, 89 received a conforming product and one received a non-conforming product.
- Overall, 97% (89/92) of the subjects randomized to the lisocabtagene maraleucel arm received conforming product, one subject received a non-conforming product.

Standard therapy arm

- In the control arm, 91 (99%) subjects started treatment and one (1%) subject withdrew consent before starting standard therapy due to COVID-19.
- Out of the 91 subjects who started standard therapy, 43 subjects received HDCT and 43 (46%) underwent HSCT treatment. One subject received HDCT but was not reported as having HSCT because subject received last dose of HDCT on the cutoff date.
- Forty-eight (53%) subjects did not proceed to start HDCT and discontinued from the treatment period. The most common reasons for discontinuation were lack of efficacy (29%), followed by disease relapse (19%).
- In the standard therapy arm, 50 subjects (54%) crossed over to the lisocabtagene maraleucel arm after IRC confirmation of a qualifying event. Among these 50 subjects, 46 subjects received the lisocabtagene maraleucel infusion.
- Overall, 46% of the subjects randomized to the standard therapy arm received definitive therapy in the control arm.

Reviewer comment(s)

There was a clear difference between two arms in the number of subjects who complete the definite therapy. In the lisocabtagene maraleucel arm, 97% of the randomized subjects were able to receive definitive therapy compared to 46% of the randomized subjects in the standard therapy arm. This highlights the multistep nature of the standard therapy arm and chemo refractory nature of the study population. 54% of the subjects in the standard therapy arm crossover to lisocabtagene maraleucel could indicate investigator bias for the efficacy of the novel CAR-T cell therapy.

Protocol Violations/Deviations

In the ITT analysis set, a total of nine (10%) subjects in the lisocabtagene maraleucel arm and nine (10%) subjects in the standard therapy arm had at least one important protocol

deviation Table 5. The most frequently reported important protocol deviation was in the other category, specifically, failure to report SAEs/suspected unexpected serious adverse reaction (SUSARs) (9 [10%] subjects in the standard therapy arm and 8 [9%] subjects in the lisocabtagene maraleucel arm). None of the important protocol deviations were related to eligibility criteria and none were attributed to COVID-19.

Table 5: Protocol Deviations in Study BCM-003.

Category	Lisocabtagene Maraleucel Arm N=92 n (%)	Standard Arm N=92 n (%)	Total N=184 n (%)
Number of subjects with at least one IPD	9 (10)	9 (10)	18 (10)
IPD			
Visit schedule	2 (2)	0	2 (1)
Missing safety or efficacy assessment	1(1)	0	1 (0.5)
Visit(s) performed outside protocol windows	1(1)	0	1 (0.5)
Other	8 (9)	9 (10)	17 (10)
Failure to report SAEs/SUSARs per regulations	8 (9)	9 (10)	17 (10)
Number of subjects with			
One IPD	7(8)	9 (8)	14 (8)
Two IPDs	1(1)	2 (2)	3 (2)
More than two IPDs	1(1)	0	1 (0.5)

IPD = Important Protocol Deviation; ITT = intent-to-treat; N = number of subjects in analysis set; n (%) = number (percentage) of subjects; SAE = serious adverse event; SOC = system organ class; SUSAR = suspected unexpected serious adverse reaction.
(Source: Clinical Study Report BCM-003)

Reviewer comment(s)

The small number and the nature of the violations/deviations, as described above, are unlikely to have any substantial impact on the efficacy results of Study BCM-003.

- **6.1.11 Efficacy Analyses**

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis endpoint in the ITT population in Study BCM-003 was EFS which was defined as the time from randomization to death from any cause, progression, failure to achieve CR or PR by 9 weeks post-randomization (after three cycles of standard chemotherapy for the standard therapy arm and 5 weeks after lisocabtagene maraleucel infusion for lisocabtagene maraleucel arm) or start of new antineoplastic therapy due to efficacy concerns whichever comes first.

The results from Study BCM-003 submitted in this application were based on a prespecified interim analysis, planned at 80% of information fraction and executed at 82% of information fraction, with the significance threshold being a one-sided alpha of 0.012. Table 6 summarizes the EFS result in the ITT analysis set per IRC-FDA and IRC assessment, respectively.

Table 6: EFS Results per IRC-FDA and IRC (ITT Analysis Set) in Study BCM-003 (N = 184)

	IRC-FDA algorithm		IRC assessment	
	Lisocabtagene Maraleucel Arm, N=92	**Standard Arm, N=92**	**Lisocabtagene Maraleucel Arm, N=92**	**Standard Arm, N=92**
Number of events, n (%)	38 (41%)	60 (65%)	35 (38%)	63 (69%)
Progression	31 (34%)	43 (47%)	26 (28%)	39 (42%)
Death	2 (2%)	2 (2%)	2 (2%)	2 (2%)
Failure to achieve CR or PR by 9 Weeks post-randomization	3 (3%)	14 (15%)	4 (4%)	17 (19%)
Start a new antineoplastic therapy due to efficacy concerns	2 (2%)	1 (1%)	3 (3%)	5 (5%)
Censored, n (%)	54 (59%)	32 (35%)	57 (62%)	29 (32%)
No baseline, or no post-baseline response assessment and no death	2 (2%)	4 (4%)	2 (2%)	1 (1%)
No death, no PD, no failure to achieve CR or PR by 9 weeks post-randomization and no start of new antineoplastic therapy due to efficacy concerns	52 (57%)	28 (30%)	55 (60%)	28 (30%)
Time to EFS event (months) [a]				
median	9.5	2.4	10.1	2.3
95% CI	(5.8, NR)	(2.2, 4.6)	(6.1, NR)	(2.2, 4.3)
Follow-up (months) [b]				
median	8.2	8.4	7	10.9
95% CI	(6, 11)	(6, 12)	(6, 11)	(6, 12)
Kaplan-Meier estimate of EFS at [c]				
6 months (95% CI)	60 (48, 70)	36 (25, 46)	63 (51, 74)	33 (23, 44)
12 months (95% CI)	42 (28, 56)	25 (15, 37)	45 (29, 59)	24 (14, 35)
24 months (95% CI)	36 (20, 52)	19 (8, 34)	38 (21, 55)	18 (7, 32)
Stratified Cox PH model (lisocabtagene maraleucel arm versus standard arm)				
HR (95% CI)	0.4 (0.26, 0.60)		0.34 (0.22, 0.52)	
One-sided p-value	< 0.0001		< 0.0001	

Abbreviations: Cox PH = Cox proportional hazards
a KM product limit estimates using log-log transformation.
b Reverse KM method.
c CI calculated using Greenwood's formula.
(Source: FDA statistical reviewer's analysis)

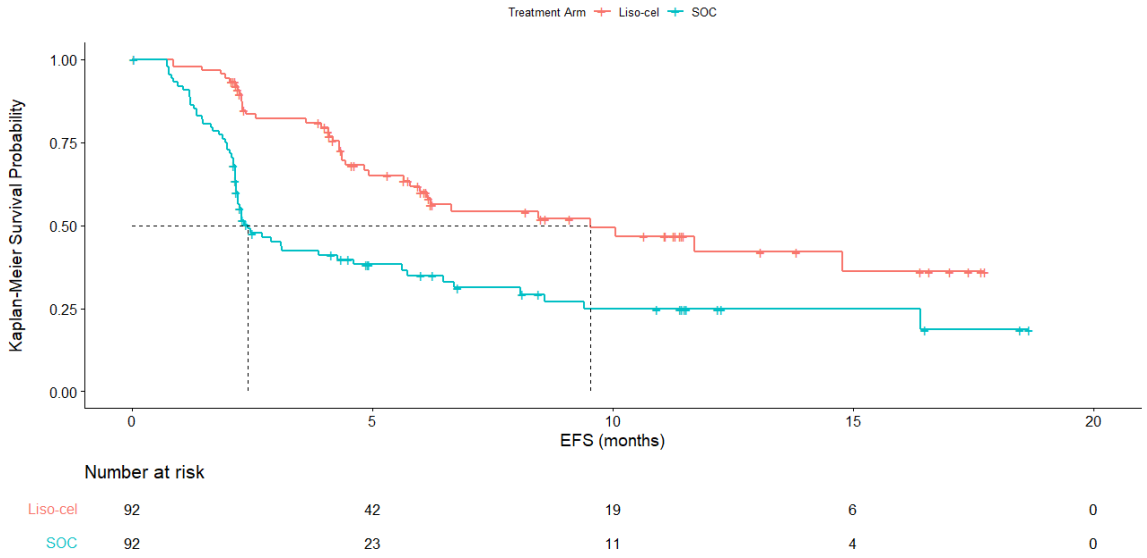
For analysis of EFS per IRC-FDA algorithm, the overall median was 9.5 months with a lower 95% limit of 5.8 months and an unattainable upper limit in the lisocabtagene maraleucel arm; and the overall median was 2.4 months with a lower 95% limit of 2.2 months and an upper limit of 4.6 months in the standard therapy arm. The subjects in the lisocabtagene maraleucel arm had substantially longer median EFS than those in the standard therapy arm. Based on the result from the stratified Cox-PH model, the lisocabtagene maraleucel arm demonstrated a statistically significant improvement in EFS based on IRC-FDA assessment compared to the standard therapy arm: HR = 0.4 (95% CI: 0.26, 0.60); one-sided p-value < 0.0001. This is similar to the EFS result by IRC assessment.

Reviewer comment(s)

- *The primary endpoint of EFS was significantly improved in the lisocabtagene maraleucel arm compared to the standard therapy arm. Treatment with lisocabtagene maraleucel resulted in a median EFS of 10.1 months vs 2.3 months with the standard therapy arm (hazard ratio [HR] = 0.34; P < .0001). This improvement is statistically as well as clinically significant.*
- *The primary analysis in this clinical review was based on IRC-FDA algorithm, however we found negligible difference between this and the IRC assessment and hence, we decided to use the IRC assessment for reporting of the primary endpoints.*

Figure 3 shows KM curve of EFS per IRC-FDA algorithm in the ITT analysis set by treatment arm. The subjects in the lisocabtagene maraleucel arm had substantially longer EFS than those in the standard therapy under both assessments.

Figure 3: KM Curve of EFS per IRC-FDA (ITT Analysis Set) In Study BCM-003.

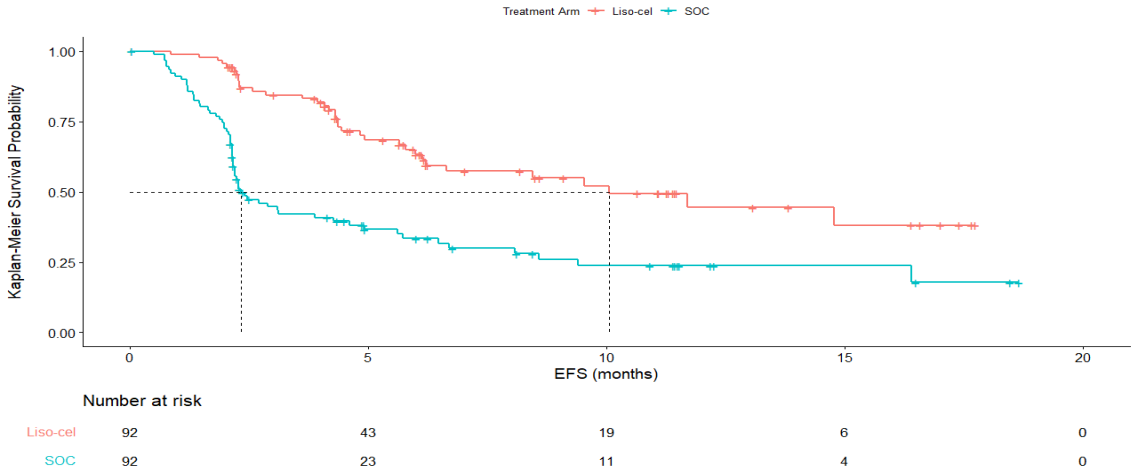


Abbreviations: IRC-FDA = FDA algorithm assessment; ITT = intent-to-treat; Liso-cel = lisocabtagene maraleucel; SOC = standard therapy.
(Source: FDA statistical reviewer's analysis)

Figure 4 shows the KM curve of IRC-assessed EFS in the ITT analysis set by treatment

arm. The subjects in the lisocabtagene maraleucel arm had substantially longer EFS than those in the standard therapy under both assessments.

Figure 4: KM Curve of EFS per IRC (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy

(Source: FDA statistical reviewer's analysis).

Reviewer comment(s)

- *In the analysis of EFS assessed by blinded central review, patients who did not meet the criteria for an event had their data censored. In the lisocabtagene maraleucel arm, 35 (38%) patients had an event; 26 (28%) had progression, 3 (3%) started a new antineoplastic therapy, and 2 (2%) died. In the standard therapy arm, 63 (69%) patients had an event; 39 (42%) had progression, 17 (19%) fail to achieve CR or PR by 9 weeks had 5(%) started a new antineoplastic therapy, and 6 (4%) died.*
- *The Kaplan Meier (KM) median EFS is longer in the lisocabtagene maraleucel arm (10.1 months [95% CI 6.1, NR]) than the standard therapy arm (2.3 months [95% CI 2.2, 4.3]) under IRC-FDA and IRC assessments.*

6.1.11.2 Analyses of Secondary Endpoints

The interim analysis of key secondary endpoints (CR rate, PFS, and OS) were prespecified, with a significance threshold of 0.012.

Complete response rate (CRR):

Table 7 summarizes the best overall response (BOR) including CR rate per the IRC-FDA algorithm and IRC assessment. The results of the two approaches were similar. The lisocabtagene maraleucel arm had statistically significantly higher CR rate than the standard therapy arm. For the IRC assessment, the CR rate was 66% (95% CI: 56, 76) in the lisocabtagene maraleucel arm and 39% (95% CI; 29, 50) in the standard therapy arm; the difference in CR rate between arms was 27% (95% CI: 12, 41) with a one-sided p-value <0.0001.

Table 7: Overall Response Rate per IRC-FDA and IRC (ITT Analysis Set) in Study BCM-003.

	IRC-FDA algorithm		IRC assessment	
	Lisocabtagene Maraleucel Arm, N=92	**Standard Arm, N=92**	**Lisocabtagene Maraleucel Arm, N=92**	**Standard Arm, N=92**
ORR (CR+PR), n (%)	**74 (80%)**	**43 (47%)**	**79 (84%)**	**44 (48%)**
95% CI	(71%, 88%)	(36%, 57%)	(77%, 93%)	(37%, 59%)
CR, n (%)	**59 (64%)**	**36 (39%)**	**61 (66%)**	**36 (39%)**
95% CI	(54%, 74%)	(29%, 50%)	(56%, 76%)	(29%, 50%)
Stratified one-sided p-value*	0.0001		<0.0001	
PR, n (%)	15 (16%)	7 (8%)	18 (20%)	8 (9%)
95% CI	(9%, 26%)	(3%,15%)	(12%, 29%)	(4%, 16%)
SD, n (%)	2 (2%)	17 (19%)	4 (4%)	21 (23%)
PD, n (%)	13 (14%)	29 (32%)	6 (7%)	24 (26%)
NE, n (%)	3 (3%)	3 (3%)	3 (3%)	3 (3%)

** By Cochran-Mantel-Haenszel test*
(Source: FDA statistical reviewer's analysis).

Progression Free Survival

Table 8 summarizes the PFS result in the ITT analysis set per IRC-FDA and IRC.

Table 8: PFS per IRC-FDA and IRC (ITT Analysis Set) in Study BCM-003.

	IRC-FDA algorithm		IRC assessment	
	Lisocabtagene Maraleucel N=92	**Standard Arm, N=92**	**Lisocabtagene Maraleucel, N=92**	**Standard Arm, N=92**
Number of events, n (%)	34 (37.0%)	46 (50.0%)	28 (30.4%)	43 (46.7%)
Progression	32 (34.8%)	44 (47.8%)	26 (28.3%)	41 (44.6%)
Death	2 (2.2%)	2 (2.2%)	2 (2.2%)	2 (2.2%)
Censored, n (%)	58 (63.0%)	46 (50.0%)	64 (69.6%)	49 (53.3%)
No baseline, or no post-baseline response assessment and no death	2 (2.2%)	4 (4.3%)	2 (2.2%)	2 (2.2%)
No death or no PD	53 (57.6%)	29 (31.5%)	56 (60.9%)	29 (31.5%)
Start of a new antineoplastic therapy before death or PD	3 (3.3%)	13 (14.1%)	6 (6.5%)	18 (19.6%)
Time to PFS event (months)				
median	11.7	5.6	14.8	5.7
95% CI	(6.1, NR)	(3.1, 8.6)	(6.6, NR)	(3.9, 9.4)

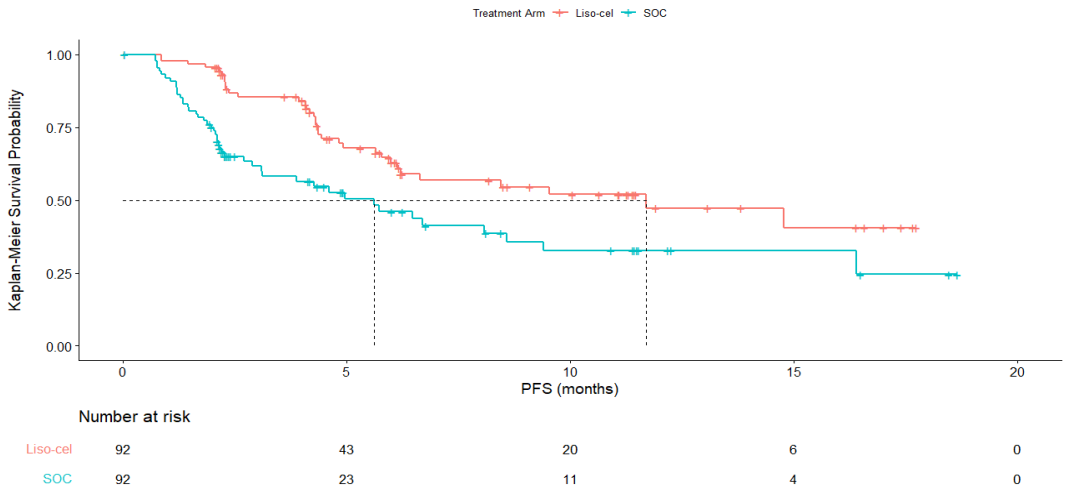
	IRC-FDA algorithm		IRC assessment	
	Lisocabtagene Maraleucel N=92	**Standard Arm, N=92**	**Lisocabtagene Maraleucel, N=92**	**Standard Arm, N=92**
Follow-up (months)				
median	8.2	4.9	6.2	4.9
95% CI	(6.0, 11.1)	(4.1, 11.1)	(5.7, 9.1)	(2.7, 8.4)
KM estimate of PFS at:				
6 months (95% CI)	63 (50, 73)	46 (34, 58)	69 (57, 79)	48 (35, 60)
12 months (95% CI)	47 (32, 61)	33 (20, 46)	52 (36, 66)	34 (21, 48)
24 months (95% CI)	41 (23, 57)	25 (10, 43)	45 (26, 62)	25 (10, 44)
Stratified Cox-PH model (lisocabtagene maraleucel arm versus Standard Arm)				
HR (95% CI)	0.47 (0.29, 0.73)		0.41 (0.25, 0.66)	
One-sided p-value	0.0004		0.0001	

Abbreviations: KM = Kaplan Meier; PD = Disease progression
(Source: FDA statistical reviewer's analysis)

Based on the result from the stratified Cox-PH model, the lisocabtagene maraleucel arm demonstrated a statistically significant improvement in PFS based on IRC-FDA compared to standard therapy: HR = 0.47 (95% CI: 0.29, 0.73); p-value = 0.0004, similar to the IRC-assessed PFS result.

Figure 5 shows KM curve of PFS per IRC-FDA (ITT analysis set) in Study BCM-003.

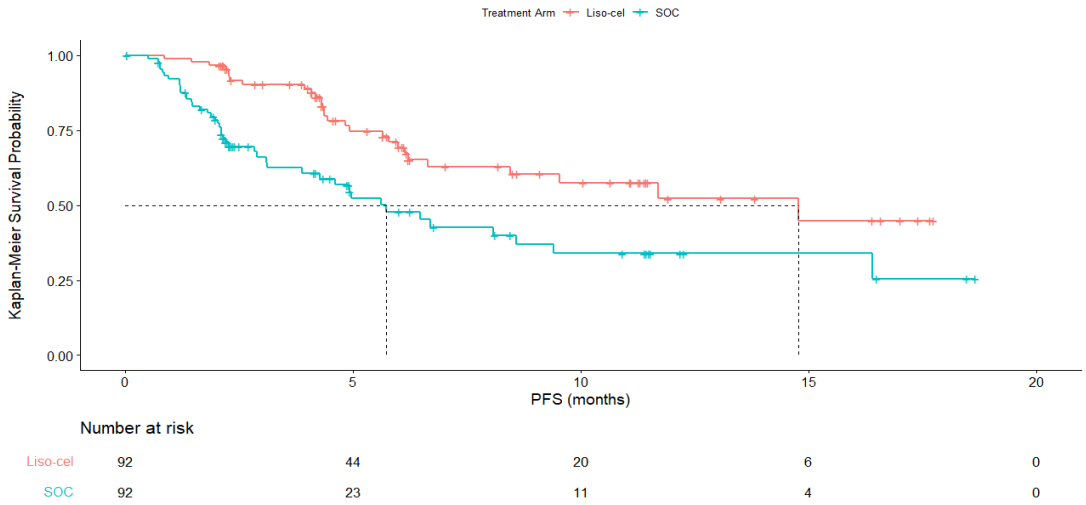
Figure 5: KM Curve of PFS per IRC-FDA (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy arm;
(Source: FDA statistical reviewer's analysis)

Figure 6 shows KM curve of PFS per IRC assessment (ITT analysis set) in Study BCM-003.

Figure 6: KM Curve of PFS per IRC (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy arm
(Source: FDA statistical reviewer's analysis)

Reviewer comment(s)

Most subjects in the lisocabtagene maraleucel arm were censored due to ongoing responses; subjects in the standard therapy arm had higher number of events, driven by progressive disease, therefore PFS was longer in the lisocabtagene maraleucel arm. The PFS data support the clinical efficacy of lisocabtagene maraleucel compared to standard therapy and it was consistent with EFS and ORR.

Overall Survival

The overall median was unattainable with a lower 95% limit of 15.8 months and an unattainable upper limit in the lisocabtagene maraleucel arm; and the overall median was 16.4 months with a lower 95% limit of 11.0 months and an unattainable upper limit in the standard therapy. Based on the result from the stratified Cox-PH regression model, the lisocabtagene maraleucel arm did not demonstrate a statistically significant improvement in OS compared to the standard therapy based on the ITT principle, although a numerical trend in favor of the lisocabtagene maraleucel arm was observed from Figure 7: HR = 0.509 (95% CI: 0.258, 1.004); one-sided p-value = 0.0257 (significance threshold, 0.012).

Table 9 summarizes the OS result in the ITT analysis set.

Table 9: Overall Survival Data (ITT Analysis Set) in Study BCM-003.

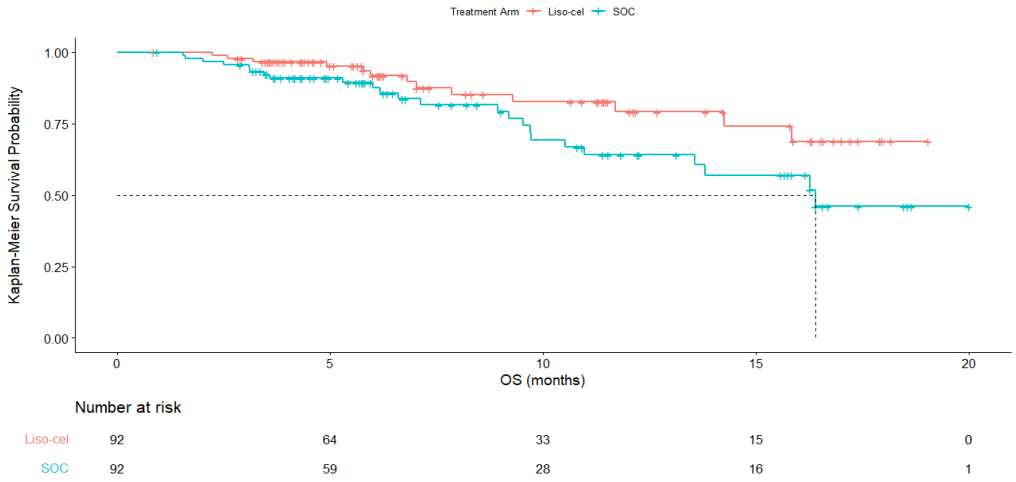
	Lisocabtagene Maraleucel Arm N=92	**Standard Therapy Arm N=92**
Death, n (%)	13 (14.1%)	24 (26.1%)
Censored, n (%)	79 (85.9%)	68 (73.9%)
Time to OS event (months)		
median	NR	16.4
95% CI	(15.8, NR)	(11.0, NR)
Follow-up (months)		
median	7	7.9
95% CI	(6.0, 11.3)	(5.8, 11.4)
KM Estimate of OS at:		
6 months (95% CI)	92 (82, 96)	89 (81, 94)
12 months (95% CI)	79 (64, 89)	64 (49, 76)
24 months (95% CI)	69 (49, 82)	46 (27, 63)
Stratified Cox-PH model (lisocabtagene maraleucel arm versus standard therapy arm)		
HR (95% CI)	0.51 (0.26, 1.00)	
One-sided p-value	0.0257	

(Source: FDA statistical reviewer's analysis)

The median OS, evaluated on interim analysis, was not reached in the lisocabtagene maraleucel arm and was 16 months in the standard therapy arm HR for death, 0.51; 95% CI, 0.26 to 1; P=0.0257 [one-sided], statistical significance not met). Overall, 13 patients (14%) in the lisocabtagene maraleucel arm and 24 (26%) in the standard therapy arm died from any cause.

Figure 7 shows the KM estimate of OS in Study BCM-003.

Figure 7: KM Curve of OS (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy arm.
(Source: FDA statistical reviewer's analysis)

Reviewer comment(s)

- *The lisocabtagene maraleucel arm did not demonstrate a statistically significant improvement in the OS compared to standard therapy arm, however the trend of the observed treatment effect is consistent with the EFS and PFS data.*
- *There is no detriment to OS in second-line use of lisocabtagene maraleucel compared to standard therapy. It is important to mention that 47 (52%) of the subjects randomized to the standard therapy were allowed to crossover and 46 (50%) of those subjects received conforming lisocabtagene maraleucel.*
- *It is possible that, with further follow-up, a statistically significant OS advantage in the lisocabtagene maraleucel arm may emerge. Please refer to Section 6.1.9 for the timeline of prespecified updates to OS.*

Duration of Response

For analysis of duration of response (DOR) per IRC-FDA algorithm, the overall median was 12.6 months with a lower 95% limit of 5.7 months and an unattainable upper limit in the lisocabtagene maraleucel arm; and the overall median was 14.5 months with a lower 95% limit of 4.7 months and an unattainable upper limit in the standard therapy. Based on the result from the stratified Cox-PH model, the lisocabtagene maraleucel arm did not demonstrate a statistically significant improvement in DOR based on IRC-FDA assessment compared to the standard therapy: HR = 0.831 (0.424, 1.630); p-value = 0.295. This is similar to the results of DOR by IRC assessment (Table 10).

Table 10: DOR per IRC-FDA and IRC (ITT analysis set) in Study BCM-003.

	IRC-FDA algorithm		IRC assessment	
	Lisocabtagene Maraleucel Arm N=92	**Standard Therapy Arm N=92**	**Lisocabtagene Maraleucel Arm N=92**	**Standard Therapy Arm N=92**
Number of subjects achieved CR or PR, n	74	43	79	44
Number of events, n (%)	21 (23%)	15 (16%)	22 (24%)	16 (17%)
Progression	18 (20%)	14 (15%)	18 (20%)	14 (15%)
Death	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Start a new anti-cancer therapy due to efficacy concerns	2 (2%)	0	3 (3%)	1 (1%)
Censored, n (%)	53 (58%)	28 (30%)	57 (62%)	28 (30%)
No response assessment after first response and no death	12 (13%)	6 (6.5%)	14 (15%)	6 (6.5%)
No death or no PD	41 (44.6%)	22 (24%)	43 (47%)	22 (24%)
DOR (months)				
median	12.6	14.5	12.6	14.5
95% CI	(5.7, NR)	(4.7, NR)	(5.7, NR)	(4.2, NR)
range	0.03+, 15.64+	0.03+, 17.02+	0.03+, 15.64+	0.03+, 17.02+
Follow-up (months)				
median	6.1	6.4	4.3	6.4
95% CI	(3.6, 8.9)	(3.8, 9.6)	(3.6, 6.9)	(3.8, 9.6)
DOR rate at:				
6 months (95% CI)	64.5 (49, 76)	65.9 (47, 80)	64 (49, 76)	64 (45, 78)
12 months (95% CI)	57.8 (42, 71)	52.1 (32, 69)	58 (41, 71)	51 (31, 68)
24 months (95% CI)	49.6 (29, 67)	34.7 (9, 63)	49 (29, 67)	34 (9, 62)
Stratified Cox-PH model (lisocabtagene maraleucel arm versus standard therapy)				
HR (95% CI)	0.83 (0.42, 1.63)		0.79 (0.41, 1.51)	
One-sided p-value	0.295		0.236	

(Source: FDA statistical reviewer's analysis)

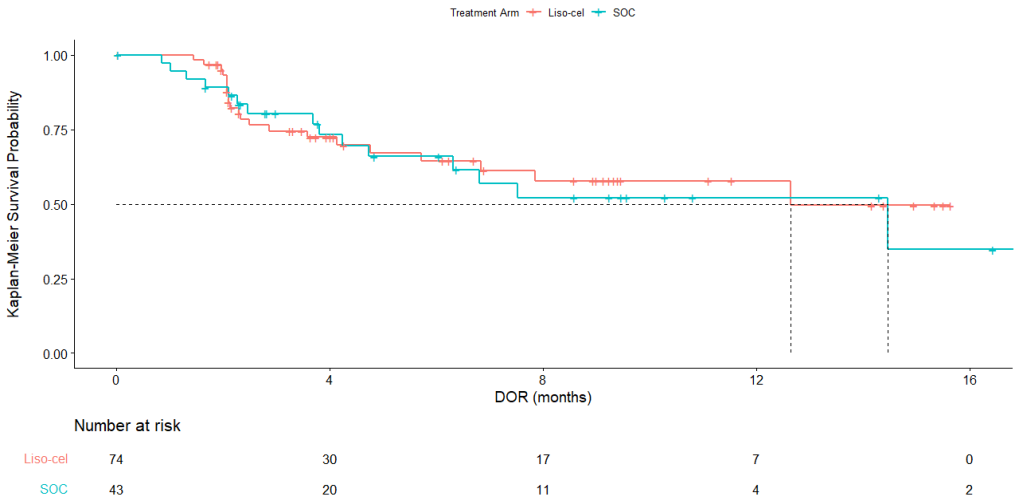
Reviewer comment(s)

- *The estimated median DOR was 12.6 months in the lisocabtagene maraleucel arm (95% 5.7, NR), and the estimated median DOR was 14.5 months in the standard therapy arm (95% 4.7, NR) with a median follow-up time for DOR using reverse KM method of 4.3 months and 6 months, respectively.*
- *The DOR analysis between two arms does not compare a well-balanced population in terms of prognostic factors; it only compares responders which is not*

an adequate efficacy analysis.

Figure 8 shows KM curve of DOR per IRC-FDA algorithm in the ITT analysis set by treatment arm.

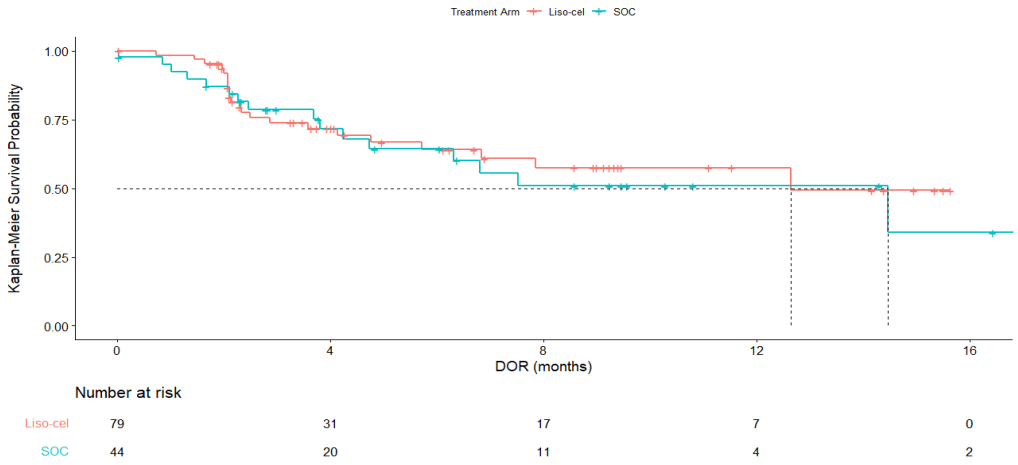
Figure 8: KM Curve of DOR per IRC-FDA (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy arm.
(Source: FDA statistical reviewer's analysis)

Figure 9 shows KM curve of DOR per IRC assessment in the ITT analysis set by treatment arm.

Figure 9: KM Curve of DOR per IRC (ITT Analysis Set) in Study BCM-003.



Abbreviations: Liso-cel = lisocabtagene maraleucel; SOC = standard therapy arm.
(Source: FDA statistical reviewer's analysis)

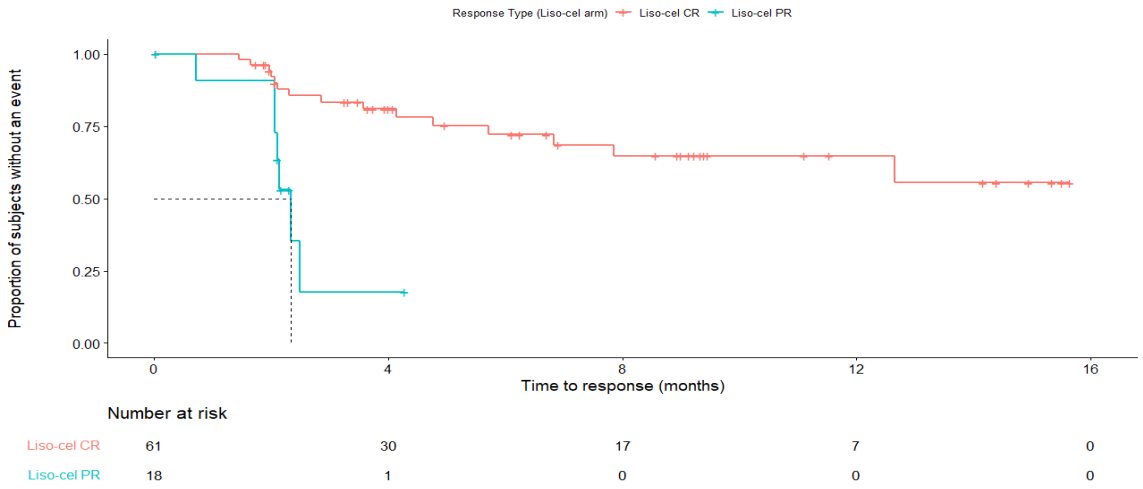
A standalone analysis of DOR in the lisocabtagene maraleucel arm was performed to evaluate DOR according to best overall response. Table 11 and
Figure 10 show KM estimates of DOR based on depth of response in the lisocabtagene maraleucel arm.

Table 11: DOR Based on Depth of Response per IRC in Study BCM-003.

Parameter	Lisocabtagene Maraleucel Arm		
	CR, n=61	PR, n=18	Overall, n=79
Median DOR (95% CI)	NR (7.85, NR)	2.33 (2.07, NR)	12.65 (5.72, NR)
Range	0.03+, 15.64+	0.03+, 4.27+	0.03+, 15.64+
DOR rate at:			
≥ 12 months (95% CI)	64.8 (46.8, 78.0)	17.7 (1.0, 52.5)	57.5 (41.5, 70.7)
≥ 24 months (95% CI)	55.6 (32.1, 73.8)	17.7 (1.0, 52.5)	49.3 (28.9, 66.8)

(Source: FDA statistical reviewer's analysis)

Figure 10: KM Plot of DOR in CR vs PR in Lisocabtagene Maraleucel Arm per IRC in Study BCM-003.



(Source: FDA statistical reviewer's analysis)

Reviewer comment(s)

The DOR correlates with depth of response; complete responders tended to have substantially longer DOR than the partial responders, which is consistent with the third-line setting as well as outcomes with other autologous anti-CD19 CAR-T cell products approved for LBCL.

Patient-Reported Outcomes (PROs)

Health-related quality of life (HRQoL) was assessed as a secondary endpoint based on changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ- C30, the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L. Numbers of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization were also assessed.

Reviewer comment(s)

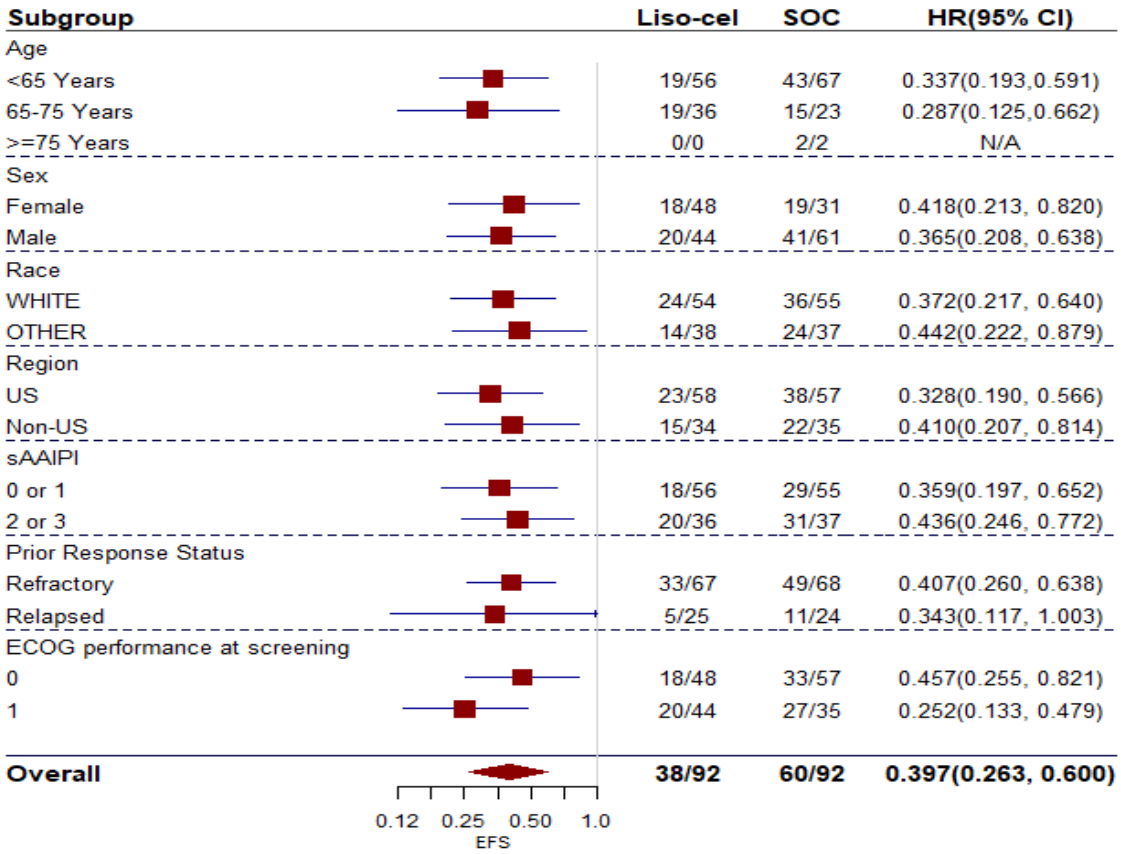
The Applicant did not seek a labeling claim based on HRQoL data and these data were not incorporated in the PI. The data were not evaluated as part of the application review, given the limitations of HRQoL assessments in uncontrolled, open-label trials. Hence, the

clinical reviewer did not perform any assessment to inform safety/efficacy based on PRO endpoints.

6.1.11.3 Subpopulation Analyses

Figure 11 shows Forest plot of EFS result across subgroups in Study BCM-003.

Figure 11: Forest Plot of EFS Result Across Subgroups in Study BCM-003.



Abbreviations: liso-cel = lisocabtagene maraleucel; sAAIPI = (secondary) age adjusted international prognostic index; SOC = standard therapy arm.
(Source: FDA statistical reviewer's analysis)

Reviewer comment(s)

- *The primary endpoint of EFS is significantly enhanced in the lisocabtagene maraleucel arm compared with the standard therapy arm across most subgroups including primary refractory versus relapsed disease.*
- *Subgroups with small sample size such as African American race and "other" histological subtypes are difficult to evaluate given the small sample size. Therefore, meaningful conclusion regarding efficacy in these subgroups cannot be made.*

6.1.11.4 Dropouts and/or Discontinuations

Table 12 shows reasons for discontinuations on Study BCM-003.

Table 12: Discontinuations from Treatment on Study BCM-003.

Reason for Discontinuation	Standard Therapy Arm	Lisocabtagene Maraleucel Arm	
		Before Lisocabtagene Maraleucel	After Lisocabtagene Maraleucel
Consent withdrawal	1	1	N/A
Manufacturing failure	N/A	1	N/A
Adverse events	1	N/A	N/A
Death	2	N/A	3
Disease relapse	17	N/A	6
Lack of efficacy	26	N/A	N/A
Physician decision	3	N/A	N/A

(Source: Modified from CSR, BCM-003, Figure 2)

Reviewer comment(s)

The dropouts/ discontinuations did not affect the overall results of the study since this is a randomized trial. The randomization will balance the time to endpoint assessment and since the primary endpoint was EFS, the randomization will minimize bias resulting from dropouts/ discontinuation.

6.1.11.5 Exploratory and Post Hoc Analyses: Not applicable

- **6.1.12 Safety Analyses**

6.1.12.1 Methods

The key materials used for the safety review included:

- The BLA application electronic submission.
- Applicant submissions in response to the review team's information requests.
- Proposed labeling for lisocabtagene maraleucel.
- Published literature.
- Prior regulatory history.
- The clinical review of safety was primarily based upon analysis of 89 subjects in the lisocabtagene maraleucel arm in Study BCM-003 at the primary data cutoff of March 8, 2021. The lisocabtagene maraleucel analysis datasets (ADaM datasets) were used for the safety analysis. Analyses by the clinical reviewer for safety were performed using JMP 16. All narratives and relevant case report forms (CRFs) were reviewed for all serious adverse events (SAEs) and deaths that occurred in the primary safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) severity was graded as a syndrome according to a modification of the 2014 Lee criteria grading system. The modification of the Lee criteria is that neurologic AEs were not taken into account in CRS grading of organ toxicity since neurologic toxicity is now considered a distinct entity. Some AEs are presented throughout this review as grouped terms as defined by the review team. The complete list of FDA's grouped terms is presented in Appendix 1. Unless

otherwise specified, all analyses and tables were generated by the FDA clinical reviewer and/or the safety review team.

- The safety analysis set included all subjects treated with one dose of conforming lisocabtagene maraleucel product. All AEs were collected from the start of leukapheresis until 90 days after lisocabtagene maraleucel infusion.
- Serious adverse events (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, resulted in persistent or significant disability, resulted in congenital anomaly or birth defect, or resulted in any other medically important serious event. SAEs were collected from the time of screening.
- Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring or worsening on or after the randomization and within 90 days after the infusion of lisocabtagene maraleucel or start of new antineoplastic therapy, whichever occurs first as those AE made known to the investigator at any time thereafter that are suspected of being related to study treatment of lisocabtagene maraleucel administration through and including 90 days after final cycle of JCAR017. The adverse event reporting periods with the data collected during these periods is shown in Table 14. Within the time periods, AEs were mapped as follows: 1) from randomization to LD chemotherapy 2) from LD chemotherapy to lisocabtagene maraleucel infusion (LDC) 3) start of LDC to the day before 1st lisocabtagene maraleucel infusion 4) lisocabtagene maraleucel first infusion upto and including 90 days (TEAE).
- The following AEs were to be reported as SAEs from time of lymphodepleting chemotherapy: secondary malignancies, new onset, or exacerbation of pre-existing-neurologic, rheumatologic, or autoimmune disorder, new onset of hematologic disorder and rare and unexpected disorders with an unknown etiology e.g. Guillain-Barre syndrome.

Reviewer comment(s)

- *The safety of chemoimmunotherapy followed by HDT and HSCT (standard therapy arm) is already established, therefore the safety analysis in this review focuses on the results of lisocabtagene maraleucel arm.*
- *The following are other considerations confirming the limited utility of a comparative toxicity analysis between the two arms: 1) Significant heterogeneity in the standard therapy arm in terms of exposure, the toxicities reported for this arm do not reflect the intended treatment plan and are likely underrepresented 2) The two arms have fundamentally different treatment modalities that have distinct toxicity profile rendering a comparative toxicity analysis.*

The demographic information and subject disposition for the subjects evaluated for safety are summarized in Table 13:

Table 13: Demographics and Baseline Characteristics in Study BCM-003 (Safety Analysis Set)

Characteristics	N =89 n (%)
Age (years)	
< 65	55 (62)
≥ 65 < 75	34 (38)
Mean (SD)	58 (12)
Median (range)	59 (20-74)
Sex	
Female	47 (53)
Male	42 (47)
Race	
White	52 (58)
Asian	10 (11)
Black	4 (4)
Other	2 (2)
Not reported	21 (24)
Ethnicity	
Not Hispanic or Latino	63 (71)
Hispanic or Latino	3 (3)
Unknown	63 (25)
Country	
USA	56 (63)
EU	28 (31)
Japan	5 (6)
Response to Prior Therapy	
Refractory	64 (72)
Relapsed	25 (28)
sAAIPI Score (Category)	
0 or 1	56 (63)
2 or 3	33 (37)

(Source: FDA analysis of ADAE, ADSL dataset)

6.1.12.2 Overview of Adverse Events

Detailed safety data are available for a total of 184 subjects who were included in the safety analysis set. For the purpose of this review, "Day 1" refers to the day of randomization as defined per protocol. Throughout this review, some TEAEs are presented as grouped terms (GT) as defined by FDA. The Applicant grouped certain terms when presenting the adverse reactions but didn't use the FDA GTs when analyzing all AEs. Moreover, the grouping was limited and occasionally missed cases. For example, certain AEs that were suggestive of a single clinical entity were sometimes termed using different dictionary derived terms (e.g. "neutropenia" and "neutrophil count decreased"). Therefore, the reviewer used a different grouping strategy for comprehensive analyses of AEs. The overall GTs are aligned with what has been used in the review of other similar approved products. Please refer to Appendix 1 for full list of FDA Grouped Terms (GTs).

AEs and deaths were also assessed for the period from randomization (i.e., leukapheresis) to the planned time of infusion to assess risks for subjects who did not receive lisocabtagene maraleucel due to manufacturing issues or adverse events, however due to minimal number of manufacturing failures in Study BCM-003 this analysis

will not relevant information.

All 89 subjects (100%) had at least one TEAE. An overview of all AEs with a data cutoff date of 08 March 2021 is presented in Table 14. The majority of the maximum toxicity grades were Grade 3 and 4 events.

Table 14: Summary of Treatment -Emergent Adverse Events in Study BCM-003 (N = 89).

Parameter	Lisocabtagene Maraleucel N = 89 n (%)
All Grade AEs	89 (100)
Max Grade 3-5 AEs	82 (92)
Max Grade 3 AEs	8 (9)
Max Grade 4 AEs	73 (82)
Max Grade 3 or 4 AEs	81 (91)
AEs leading to death*	2 (2)
SAEs	41 (46)

Abbreviations: AE = adverse events; SAE = serious adverse events
**Excludes death from progressive disease*
(Source: FDA Analysis of ADAE, ADSL dataset)

Reviewer comment(s)

Information requests were sent the Applicant to verify and re-adjudicate AEs. The reviewer requested the resubmission of updated datasets (ADAE, ADSL) that reflect FDA's review and re-adjudication and FDA GT.

Incidence of AEs are presented by system organ class (SOC) and also by the individual AEs. Table 15 details AEs by SOC that occurred in ≥ 10% of subjects

Table 15: Treatment-Emergent Adverse Events (TEAE) in ≥ 10% of Safety Population by System Organ Class in Study BCM-003 (N = 89)

SOC / Preferred Term or FDA Grouped Preferred Term	All Grades n (%)	Grade 3 or Higher n (%)
Blood and lymphatic system disorders		
Febrile neutropenia	9 (10)	9 (10)
Cardiac disorders		
Tachycardia (GT)	13 (15)	0 (0)
Gastrointestinal disorders		
Nausea	21 (24)	0 (0)
Constipation	18 (20)	2 (2)
Diarrhea	16 (18)	0 (0)
Abdominal pain (GT)	12 (13)	2 (2)
Vomiting	10 (11)	0 (0)

SOC / Preferred Term or FDA Grouped Preferred Term	All Grades n (%)	Grade 3 or Higher n (%)
General disorders and administration site conditions		
Fever	49 (55)	3 (3.4)
Fatigue# (GT)	25 (28)	1 (1)
Edema # (GT)	12 (13)	0 (0)
Immune system disorders		
Cytokine release syndrome	44 (49)	1 (1)
Infections and infestations		
Bacterial infectious disorders (GT)	11 (12)	5 (6)
Infections - pathogen unspecified (GT)	11 (12)	5 (6)
Sepsis	10 (11)	6 (7)
Metabolism and nutrition disorders		
Decreased appetite	13 (15)	0 (0)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain (GT)	32 (36)	3 (3)
Motor dysfunction (GT)	11 (12)	3 (3)
Nervous system disorders		
Headache# (GT)	30 (34)	5 (6)
Dizziness (GT)	18 (20)	1 (1)
Tremor (GT)	10 (11)	1 (1)
Psychiatric disorders		
Insomnia (GT)	13 (15)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Cough (GT)	10 (11)	0 (0)
Skin and subcutaneous tissue disorders		
Rash (GT)	11 (12)	1 (1)
Vascular disorders		
Hypotension (GT)	13 (15)	2 (2)
Hemorrhage (GT)	11 (12)	0 (0)

Abbreviation: GT: grouped term, as defined in Appendix 1
 # Encompasses more than one SOC.
(Source: FDA analysis of ADAE, ADSL datasets)

Other clinically important adverse reactions that occurred in <10% of subjects treated with lisocabtagene maraleucel include the following*:*

- *Immune system disorders:* Hemophagocytic lymphohistiocytosis (1.1%)

- *Infections and infestations:* Viral infection (9%), fungal infection (4.5%), pneumonia (2.2%)
- *Nervous system disorders:* Encephalopathy (8%), aphasia (4.5%), peripheral neuropathy (4.5%), ataxia (3.4%), paresis (1.1%)
- *Psychiatric disorders:* Delirium (2.2%)
- *Renal and urinary disorders:* Renal failure (3.4%)
- *Respiratory, thoracic, and mediastinal disorders:* Dyspnea (8%)
- *Vascular disorders:* Thrombosis (8%), hypertension (7%)

Reviewer comment(s)

- *All grade AEs occurring in 10% or more subjects in Study BCM-003 are consistent with those seen with other anti-CD19 CAR-T products and in the Pivotal Study TRANSCEND. These AEs reflect the toxicities of the investigational protocol including lymphodepletion with fludarabine and cyclophosphamide. No new signal was observed.*
- *Although the AEs are presented by SOC, some grouped terms include more than one system and are indicated with a # sign in Table 18, e.g., encephalopathy includes the nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate e.g., rash under skin and subcutaneous disorders SOC, encephalopathy under nervous system disorders.*
- *For analyses of infection by pathogen, we included the grouped term e.g. bacterial infection but also included infections under other terms for which the organism was specified e.g. clostridium difficile was included in the calculation of bacterial infection. This was reflected in the AE high level group term (HLGT) column in the JMP datasets.*
- *We decided to report febrile neutropenia as a separate grouped term (GT) because of its relevance in clinical practice and deviating from the review of Pivotal study 017001 for its approval; febrile neutropenia was included as infections with pathogen unspecified.*
- *Pain as a grouped term was ultimately not included in the label, since we thought it was too broad a category to provide meaningful information to clinicians.*

<u>Reviewer comments pertinent to the adverse drug reaction (ADR) table of the label:</u>

The table above will serve as the basis for the ADR table of the label. The laboratory abnormalities incidence will be presented in a separate that is derived from the ADLB datasets and not from the AE datasets since the ADLB is more accurate and will capture all laboratory abnormalities rather than just the ones recorded as AEs.

The incidence of TEAEs by FDA grouped preferred terms occurring in ≥ 10% of the safety population is presented in Table 19. The most common non-laboratory AEs included: CRS, headache, musculoskeletal pain, fatigue, constipation, fever, nausea, dizziness, hypotension, decreased appetite, pain, diarrhea, encephalopathy, motor dysfunction, febrile neutropenia, abdominal pain, edema, insomnia, tachycardia, rash, tremor, sepsis.

Table 16 details AEs by grouped preferred term that occurred in ≥ 10% of subjects.

Table 16: Treatment-Emergent Adverse Events (TEAEs) in ≥ 10% of Safety Population by Grouped Preferred Term in Study BCM-003 (N=89).

Adverse Event	All Grades n (%)	Grade 3 or Higher n (%)
Fever	49 (55)	3 (3.4)
Cytokine release syndrome	44 (49)	1 (1)
Musculoskeletal pain (GT)	32 (36)	3 (3)
Headache# (GT)	30 (34)	5 (6)
Fatigue# (GT)	25 (28)	1 (1)
Nausea	21 (24)	0 (0)
Constipation	18 (20)	2 (2)
Dizziness (GT)	18 (20)	1 (1)
Abdominal pain (GT)	15 (17)	2 (2)
Diarrhea	16 (17)	0 (0)
Decreased appetite	13 (15)	0 (0)
Hypotension (GT)	13 (15)	2 (2)
Insomnia (GT)	13 (15)	0 (0)
Edema # (GT)	12 (13)	0 (0)
Rash (GT)	11 (12)	1 (1)
Bacterial infectious disorders (GT)	11 (12)	5 (6)
Infections-pathogen unspecified (GT)	11 (12)	5 (6)
Motor dysfunction (GT)	11 (12)	3 (3)
Hemorrhage (GT)	11 (12)	0 (0)
Cough (GT)	10 (11)	0 (0)
Sepsis	9 (10)	6 (7)
Febrile neutropenia	9 (10)	9 (10)
Hypertension (GT)	9 (10)	3 (3)

Abbreviations: GT= grouped term.
All adverse events are listed independently whether they were part of CRS or not.
 # Encompasses more than one SOC.
(Source: FDA analysis of ADAE, ADSL Datasets)

Leukapheresis Period

This period was defined from the day of leukapheresis until the day before the start of conditioning chemotherapy. The leukapheresis population included 92 subjects however for this analysis will include only the subjects in the safety population. Table 19 and Table 20 below summarize the AEs and SAEs, respectively that occurred in this period.

Table 17 below details AEs during the leukapheresis period in the safety population.

Table 17: Adverse Events During Leukapheresis in Study BCM-003 (N=89).

Parameter	Lisocabtagene Maraleucel n (%)
All Grade AEs	76 (85)
Max Grade 3-4 AEs	48 (55)
Max Grade 3 AEs	35 (39)
Max Grade 4 AEs	34 (38)
SAEs	10 (11)

Abbreviations used: SAE= serious adverse event.
(Source: FDA Analysis of ADAE, ADSL dataset)

From randomization to leukapheresis, the most frequently reported AEs in 20% or more of subjects were thrombocytopenia (44%), musculoskeletal pain (37%) fatigue (21%), nausea (28%) and anemia (20%).

Adverse events in subjects who received bridging therapy

Out of the 89 subjects in the safety analysis set, 58 subjects (65%) received bridging therapy. The most common bridging therapy was R-ICE. Five subjects received additional cycles of bridging chemotherapy; four subjects due to delays related to the contamination issues and one subject due to rapid disease progression. Nine subjects in the lisocabtagene maraleucel arm were PET-negative at their pre-LDC assessment after receiving bridging therapy.

Overall rates to treatment-emergent adverse events (TEAEs) were similar between subjects who received bridging therapy (n=55) and those who did not (n=31). However, rates of all grade CRS or NT (Applicant identified cases) were higher in those who received bridging therapy versus (vs) those who did not (55% vs 39%).

Table 18 below details safety summary of the bridging therapy in the safety population.

Table 18: Safety Summary of Bridging Therapy in Study BCM-003 (N=89).

Safety Parameter	Bridging Therapy Yes n (%)	Bridging Therapy No n (%)
Any TEAE	55 (95)	31 (100)
Max Grade 3-4	53 (91)	25 (81)
MAX Grade 3-5	54 (93)	25 (81)
Max Grade 5	1 (1)	0
SAEs	25 (43)	9 (29)
All grade CRS	32 (55)	12 (39)
Grade 3 or 4 CRS	1 (1)	0
Grade 5 CRS	0	0
All grade NT	8 (14)	1 (3)
Grade 3 or 4 NT	4 (7)	0
Grade 5 NT	0	0
Grade 3 or 4 infection	9 (15)	3 (9)
Grade 5 infection	0	0

**Does not include FDA adjudicated CRS, NT.*
(Source: Applicant analysis; adapted from Table 4.1.1.11 in the ISS/Module 2.7.4 SCS)

Reviewer comment(s)

Given small numbers of subjects with grade 3 and higher CRS, NT and infections in subjects who received bridging and those who did not, it is speculative to comment on the observed differences of higher number of these events in the subjects who received bridging and does not alter the safety profile of lisocabtagene maraleucel. In clinical practice, many subjects with aggressive large B-cell lymphomas will require bridging chemotherapy for tumor control, and any observed difference in safety between those who receive bridging vs those who do not will translate into any change in clinical practice.

Adverse Events in the Lymphodepletion Period

The lymphodepleting AE period was calculated from the first day of the conditioning chemotherapy administration to the day prior to lisocabtagene maraleucel infusion. Seventy of the of 89 subjects (numbers reflect those who received conforming product and continue in the study) had an AE and 46 (75%) of those were deemed related to LDC. Table 19 and Table 20 give a summary of AEs unrelated or related to LDC during this time period.

Table 19: Adverse Events in the Lymphodepletion Period in Study BCM-003 (N = 89).

Parameter	N (%)
Any AE	70 (79)
Any grade 3-4 AE	36 (40)
Any grade 5 AE	0
Any SAE	4 (4)
Any AE related to LDC	46 (75)
Any grade 3-4 AE related to LDC	24 (27)
Any grade 5 AE related to LDC	0
Any SAE related to LDC	0

(Source: FDA analysis of ADAE and ADSL dataset)

Table 20: Adverse Events in the Lymphodepletion Period > 10% of Subjects (N = 89).

Adverse Event	All Grades n (%)	Grade 3 or Higher n (%)
Nausea	29 (33)	1 (1)
Headache (GT)	14 (16)	0 (0)
Edema (GT)	12 (13)	0 (0)
Musculoskeletal (MSK) pain (GT)	10 (11)	1 (1)
Fatigue (GT)	9 (10)	0 (0)

Abbreviations: GT = grouped term
(Source: FDA analysis of ADAE dataset)

The most common AEs that occurred during this period include nausea, lymphopenia, headache, anemia, edema, MSK pain and fatigue.

Reviewer comment(s)

The toxicity profile seen is consistent with commonly anticipated AEs from lymphodepleting chemotherapy.

6.1.12.3 Deaths

Table 21 summarize all deaths in the safety population of both arms using March 08, 2021, data cut-off date (data for the primary analysis).

Table 21: Death Summary in Treatment Period in Both Arms of Study BCM-003 (N = 184).

Parameters	Lisocabtagene Maraleucel Arm N = 92	Standard Arm N = 92	Post Cross-over N = 47
Deaths Total	13 (14)	6 (9%)	18 (36)
Death from malignant disease under study, or complication due to malignant disease	7 (8)	3 (3%)	10 (20)
Death from AE (not otherwise specified)	2 (2)	3 (3%)	1 (2)
Other	3 (3)	0	3 (6)
Unknown	1 (1)	0	4 (8)

Source: FDA analysis of ADSL, ADDD datasets and safety narratives

Reviewer comment(s)

During the treatment period of the Study BCM-003 the most common cause of death was disease progression. Most of the deaths 36% (18 out of 50) in the standard therapy arm occurred after crossover and were due to disease progression Three subjects in the standard therapy arm died to due to an adverse event. Two of the deaths in the standard therapy arm and one in the lisocabtagene maraleucel arm occurred due to TEAEs.

Table 22 summarize the fatal AEs observed in both arms.

Table 22: Fatal AEs Observed in Both Arms in Study BCM-003.

	SUBJID	Adverse Events	Therapy Day of Death
Lisocabtagene Maraleucel	(b) (6)	Failure to thrive/PD	79
	(b) (6)	COVID-19	150
Standard Arm	(b) (6)	Sepsis	95
	(b) (6)	Sepsis/MOF/Cardiac Arrest	49
	(b) (6)	Acute respiratory distress syndrome	94

Source: FDA analysis of ADSL, ADD datasets and safety narratives.
Abbreviations: MOF = multiorgan failure; PD =progressive disease.

Table 23 displays a summary of Deaths from Unrelated AEs and Unknown Cause in the Observed in the lisocabtagene maraleucel on Study BCM-003 (N = 92).

Table 23: Deaths from Unrelated or Unknown Causes Observed in the Lisocabtagene Maraleucel Arm (N = 92).

SUBJID	Cause of Death Category	Unrelated AE Cause of Death	Therapy Day of Death
(b) (6)	Death from other cause	COVID-19	434
(b) (6)	Death from other cause	COVID-19	356
(b) (6)	Death from other cause	SARS-CoV-2 infection	482
(b) (6)	Unknown	N/A	181

(Source: FDA analysis of ADSL, ADD datasets and safety narratives)

Reviewer comment(s)

The reviewer reviewed all death narratives to confirm the cause of death. Relevant datasets and CRFs were reviewed as needed to reach a conclusion on cause of death. Disease progression was considered as cause of death when supported by imaging, biopsy, autopsy, or other descriptive narratives of progression of underlying malignancy.

Brief description of the two subjects who died due to Grade 5 adverse events in the lisocabtagene maraleucel arm listed below:

- *Subject* (b) (6) *was a 70-year-old male with primary diagnosis of HGBL, on study Day 69 he had an assessment of progressive disease, and ten days later the subject die (Study Day 79). As per investigator the cause of death was failure to thrive Grade 5. This reviewer does not agree with the assessment, the most likely cause of death was disease progression.*
- *Subject* (b) (6) *was a 70-year-old female with primary diagnosis of HGBL. Subject died due to COVID -19 (Grade 5) on Study Day 150.*

6.1.12.4 Nonfatal Serious Adverse Events

For this review, Serious Adverse Events (SAEs) were defined as any serious AE that occurred after the start of lisocabtagene maraleucel administration. SAEs occurred in 34 of 89 subjects (38%). Table 24 summarizes all SAEs in ≥ 2% of the safety population.

Table 24: Nonfatal SAEs in ≥ 2% of Subjects in Study BCM-003 (N = 89).

System Organ Class	N=89
Subjects with any serious TEAE	**34 (38)**
Blood and lymphatic system disorders	**14 (16)**
Febrile neutropenia	9 (10)
Neutropenia	6 (7)
Thrombocytopenia	3 (3)
Immune system disorders	**12 (14)**
Cytokine release syndrome	12 (14)
Nervous system disorders	**5 (6)**
Headache	3 (3)
Encephalopathy	2 (2)
Aphasia	2 (2)
Paresis	1 (1)

System Organ Class	N=89
Tremor	1 (1)
Infections and infestations	**14 (1)**
Sepsis	10(11)
Infections with pathogen unspecified	7 (8)
Bacterial infectious disorders	5 (6)
Viral infectious disorders	3 (3)
General disorders and administration site conditions	**4 (5)**
Fever	3 (3)
Respiratory, thoracic and mediastinal disorders	**2 (2)**
Pulmonary embolism	2 (2)

**Includes COVID-19.*
All AEs are listed independently whether they were part of CRS or not.
(Source: FDA analysis of ADAE dataset)

The most frequently reported SAE Grade 3 or higher in ≥ 2% or more of subjects in Study BCM-003 were CRS (14%), sepsis (11%), febrile neutropenia (10%), neutropenia (6%), headache (3%), thrombocytopenia (3%), encephalopathy (2%), anemia (2%) and thrombosis (2%).

Reviewer comment(s)

SAEs observed on Study BCM-003 are similar to those observed on other FDA approved CAR-T cell therapies.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest for safety analyses included infusion reaction, cytokine release syndrome (CRS), neurologic toxicity (NT), macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), infections, prolonged cytopenias not resolved by day 29 post lisocabtagene maraleucel infusion, secondary malignancies, and autoimmune events.

Cytokine Release Syndrome (CRS)

CRS occurred in 44 subjects (49%), and only one (1%) subject experienced grade 3 or higher CRS. CRS was graded per modified Lee et al 2014 criteria which excludes neurologic AEs as part of CRS. See Table 25 for details. For analyses of subjects with CRS and/or neurologic toxicities, please see neurologic toxicity in this section.

Table 25: CRS Toxicity Grade Study in Study BCM-003 (N = 89).

Worst CRS Toxicity Grade	N = 89 n (%)
CRS, Any Grade	44 (49)
Grade 1	33 (37)
Grade 2	10 (11)
Grade 3	1 (1)
Grade 4-5	0 (0)

(Source: FDA analysis of ADAE, ADSL dataset)

Median time to CRS onset was 5 days (range 1 to 63 days) (interquartile range [IQR]) of 3, 8). CRS resolved in all the subjects. Median time to onset of maximum CRS grade was 9 days. Median time duration was 4.5 days (range 1 to 16 days and IQR of 2,5).

Table 26 shows CRS Symptoms in ≥ 2% of Safety Population in Study BCM-003.

Table 26: CRS Symptoms in ≥ 2% of Safety Population in Study BCM-003 (N = 89).

CRS Symptoms / AEs	N = 89 n (%)
Fever	44 (49)
Hypotension	9 (10)
Chills	4 (4)
Headache	4 (4)
Tachycardia	2 (2)
Hypoxia	2 (2)
Transaminase elevation (GT)	2 (2)
Dizziness	2 (2)
Musculoskeletal pain (GT)	2 (2)

Abbreviations: GT: Grouped Term.
(Source: FDA analysis of ADAE dataset)

The most common reported symptoms of CRS were fever, hypotension, and chills and headache. The most frequently reported Grade ≥ 3 symptoms of CRS were fever (3%), headache (2%), and hypoxia (2%). There were no Grade 4 or Grade 5 CRS symptoms.

Reviewer comment(s)

- *Per Lee et al. 2014, clinical signs and symptoms associated with CRS may include constitutional symptoms (e.g., fever, nausea, fatigue etc.) or other organ toxicities (e.g., cardiovascular, hepatic, renal etc.). Our review strategy of finding additional subjects with CRS included identifying fever, hypotension or hypoxia between Day 0 and Day 30 in subjects who were not flagged as having CRS. We additionally looked for subjects not flagged as having CRS but who received tocilizumab, vasopressors, intravenous fluids (IVF) or oxygen.*
- *We also reviewed cytokine and laboratory data (Ferritin, C-reactive protein, IL-6 levels) for supportive evidence. Subjects who were identified to have isolated hypotension without other symptoms suggestive of CRS were not included.*

- *After reviewing all narratives and relevant CRFs and datasets, we did not adjudicate additional subjects as having CRS.*
- *In addition, CRS grading and CRS duration were reviewed, and no cases were re-adjudicated.*

CRS Management

Tocilizumab and/or corticosteroids were used in the management of CRS. The table below summarizes their use, using the total number of patients in the safety population as the denominator.

Table 27: Tocilizumab and Corticosteroid Use in CRS Management in Study BCM-003 (N = 89).

Medication	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4-5 n (%)	Overall n (%)
Tocilizumab only	8 (9)	1 (1)	N/A	0	9 (10)
Corticosteroids only	0 (0)	0 (0)	N/A	0	0 (0)
Tocilizumab and/or Corticosteroids	12 (14)	6 (7)	1 (2)	0	19 (21)
Both Tocilizumab and Corticosteroids	4 (5)	5 (6)	1 (2)	0	10 (11)
Other*	N/A	1(1)	N/A	N/A	1 (1)

(Source: Applicant analysis; response to IR # 24 Table 24.T.4.11.1.1)
** Other immunosuppressive agents given include siltuximab, anakinra, and etanercept.*

Reviewer comment(s)

Management of CRS with tocilizumab and/or corticosteroids (denominator 89 subjects in Study BCM-003) is consistent with clinical practice. Overall incidence of CRS observed in Study BCM-003 is similar to that observed in Study 17001 (49% and 36%). In general, rate of grade 3 and higher CRS was low. Lower rates of severe CRS are likely due to early recognition and intervention preventing serious toxicity and end organ damage.

Neurologic Toxicity

Among 89 treated with lisocabtagene maraleucel, 18 (20%) experienced one or more neurologic toxicity events and 4 subjects (4%) experienced Grade 3 or higher (severe or life threatening) events. The following neurologic toxicity events occurred in ≥2% of subjects: headache, encephalopathy, tremor, dizziness, aphasia, ataxia, and delirium. See Table 28 and Table 29 for details regarding NT and the individual AEs that were considered part of NT.

The median time to onset of first event was 10 days (range 1 to 25 days) (interquartile range [IQR]) of 7, 12 days). Median time to onset of maximum NT grade was 8 days (range 2 to 14 days) ([IQR]) of 8, 13 days) The median time to resolution was 11 days (range 1 to 119), (IQR of 6, 22 days). The median time duration was 11 days (range 1-155) (IQR of 6, 49 days).

Table 28: Neurologic Toxicity Grade in Study BCM-003 (N = 89).

Neurologic Toxicity Grade	N =89 n (%)
Neurologic Toxicity, Any Grade	18 (20)
Grade 1	14 (16)
Grade 2	5 (6)
Grade 3	7 (8)
Grade 4-5	0 (0)

(Source: FDA analysis of ADAE dataset)

Table 29: Neurologic Symptoms in the Safety Population in Study BCM-003 (N = 89).

Adverse Event	All Grades n (%)	Grade 3 or Higher n (%)
Headache (GT)	10 (11)	4 (4)
Tremor (GT)	9(10)	1 (1)
Dizziness (GT)	7 (8)	0 (0)
Encephalopathy (GT)	7 (8)	2 (2)
Neuropathy Peripheral (GT)	4 (4.5)	0 (0)
Aphasia	4 (4)	2 (2)
Ataxia (GT)	3 (3)	0 (0)
Delirium (GT)	2 (2)	0 (0)
Agraphia	1 (1)	0 (0)
Paresis (GT)	1 (1)	1 (1)

NT: Neurologic Toxicity; multiple events could have contributed to NT in subjects.
**GT: grouped term as defined in Appendix 1.*
(Source: FDA analysis of ADAE, ADSL dataset)

Reviewer comment(s)

- *There is a discrepancy between the numbers of all grade headache between treatment emergent headache and that listed under neurologic toxicity. This is because treatment emergent headache, includes headache from all causes e.g. CRS, general disorder, medications etc. while that described under neurologic toxicity is headache attributed to lisocabtagene maraleucel neurotoxicity.*
- *The Applicant identified 11 (12%) subjects with neurologic toxicity related to lisocabtagene maraleucel. After reviewing all narratives and relevant CRFs and datasets, we adjudicated additional 7 subjects as having neurologic toxicity the details for whom are provided in Table 30. Any grade neurologic toxicity increased to 18 subjects (20%) and Grade ≥3 neurologic toxicity increased to 7 subjects (8%).*

Table 30: FDA Adjudication: Neurologic Toxicity

USUBJID	FDA Comments	Final Re-adjudication
(b) (6)	Subject had Grade 1 dizziness, gait disturbance, tremor, headache between days 2-16 deemed to be consistent with NT due to therapy	No alternative explanation for symptoms, included as subject with NT.
(b) (6)	Subject experienced Grade 2 headache along with Grade 4 (right-sided) facial paresis. (CT) scan of the head, MRI (head), and CT angiography (head and neck) done, however results were not reported.	Multiple neurologic symptoms deemed related to the treatment
(b) (6)	Subject experienced Grade 1 balance disorder on study day 36, then on study day 42, the subject experienced Grade 1 disturbance in attention, noted as decreased concentration per physical examination.	Neurologic symptoms with sequential timeframe of occurrence consistent with NT.
(b) (6)	Subject developed Grade 3 headache, required hospitalization, lasted 5 days, no clear explanation for the events, will consider NT	Severe headache required hospitalization, with no clear alternative explanation
(b) (6)	Subjects experienced Grade 1 dizziness and MMSE score of 22/30 (mild cognitive impairment). Grade 1 headache and irritability, headache worsened to Grade 3.	Subject had multiple neurologic symptoms with sequential timeframe of occurrence and no alternative explanation.
(b) (6)	Subject developed Grade 1 tremor, followed by dizziness and peripheral neuropathy	Subject had NT symptoms with sequential timeframe of occurrence
(b) (6)	Subject had Grade 1 headache, and tremor. Overlapping neurotoxicity symptoms and indicative of neurotoxicity.	Overlapping neurologic symptoms and indicative of neurotoxicity.

Reviewer comment(s)

Although some symptoms like tremor, headache, dizziness etc. may either be less specific for immune effector cell-associated neurotoxicity syndrome (ICANS) or not require intervention if they occur in isolation, they nevertheless represent neurologic toxicity from study product and were flagged as such. We also took into consideration the timing of symptoms post study product infusion, clustering of multiple symptoms during a given time frame or sequential occurrence, and alternate explanation for symptoms prior to final adjudication.

Management of Neurologic Toxicity

Corticosteroids, antiepileptic medications, and IL-6 agents were used in NT management (Table 31). Antiseizure medications were used as prophylaxis or treatment. The table below uses the total number of subjects in the safety population as the denominator.

Table 31: Management of Neurologic Toxicity in Study BCM-003 (N = 89).

Medication	N=89 n (%)
Tocilizumab and/or corticosteroids	7 (8)
Corticosteroids only	6 (7)
Dexamethasone	6 (7)
Tocilizumab only	1 (1)
Both Tocilizumab and corticosteroids	0 (0)
Antiseizure prophylaxis	3 (4)

(*Source: FDA analysis of ADSL, ADCM dataset)*

Reviewer comment(s)

- *Neurologic toxicity consisted of different neurologic and/or psychiatric manifestations with or without overlapping time courses. Duration of NT was calculated from time of onset of the first event until resolution of the last event.*
- *Antiseizure medications used in Study BCM-003 included levetiracetam and among the 89 subjects treated with lisocabtagene maraleucel 28 (31%) received antiseizure prophylaxis.*

Neurological toxicity and CRs

Neurological toxicity started and /or ended before, during or after CRS onset and resolution. Neurotoxicity was concurrent or following onset of CRS in six subjects and predating CRS in three subjects. NT was an isolated event in nine subjects.

Infections

All grade infections including febrile neutropenia occurred in 48% (43/89) subjects with grade 3 or higher infections occurring in 17% (15/89) subjects. Table 32 details infections by broad pathogen class e.g. bacterial infections. Febrile neutropenia occurred in 9 subjects (10%). Sepsis occurred in 9 (10%) subjects.

Table 32: Treatment -Emergent Infections by HLGT in the Safety Population in Study BCM-003 (N = 89).

TEAE Infections*	All Grade n (%)	Grade3 or Higher n (%)
Bacterial infections disorders	11 (12)	5 (6)
Infections-pathogen unspecified	11 (12)	5 (6)
Febrile Neutropenia	9 (10)	9 (10)
Viral infectious disorders	8 (9)	3 (3)
Fungal infections disorders	4 (4.5)	0

** Includes infections by High Level Group Terms (HLGT).*
(Source: FDA analysis of ADAE dataset)

Reviewer comment(s)

- *Although febrile neutropenia is presented in Table 32, it was not included in the incidence of infections, and it was rather listed separately. The review of the original BLA, febrile neutropenia was included among the HLGT Infections-pathogen unspecified Grade 3 or higher only. And since not all of the FN are reported as Grade 3 or higher in this application, we considered more relevant to inform the treating physician to list FN separately.*
- *Infectious-pathogen unspecified HLGT includes a range of specific and unspecified infections. This lumped together pneumonia, otitis media, klebsiella bacteremia, sepsis, eye disorder (conjunctivitis) to mention a few resulting in overinflating*

unspecified pathogen infections.

Prolonged Cytopenias

Prolonged cytopenias are defined as neutropenia, thrombocytopenia, or anemia present at day 29 following lisocabtagene maraleucel infusion. Prolonged cytopenias is summarized in this section. Overall, the number of subjects who had worst Grade 3 or higher prolonged neutropenia, thrombocytopenia and anemia were 33 (38%), 34 (38%), and 11 (12%) subjects; respectively.

Reviewer comment(s)

- *We requested Applicant to do the analysis based on the laboratory (ADLB) dataset rather than using the adverse event dataset (ADAE dataset) since this is more accurate.*
- *Parameters for blood or platelet transfusion in determining the acceptability of hemoglobin or platelet counts for analysis were specified by the Applicant and were deemed acceptable.*
- *Prolonged neutropenia and thrombocytopenia increase risk of infection and bleeding respectively.*
- *Per CTCAE criteria, all febrile neutropenia cases will be considered Grade 3 or higher.*

Hypogammaglobulinemia

Overall 8/89 subjects (9%) had hypogammaglobulinemia (GT includes hypogammaglobulinemia and blood immunoglobulin G decreased which was defined as IgG of < 500 mg/dl).

Immunogenicity

Lisocabtagene maraleucel has the potential to induce anti-product antibodies. The incidence of anti-therapeutics antibodies (ATA) was 3% (3/ 89) treated with lisocabtagene maraleucel.

Cardiac Toxicity

The most common cardiac toxicity occurring on Study BCM-003 at any grade included tachycardia (15%) and ventricular arrhythmias (2%). Table 33 includes all cardiac adverse events.

Table 33: Cardiac Adverse Events by Preferred Term and/or GT in the Safety Population in Study BCM-003 (N = 89).

Cardiac Adverse Events	All Grades n (%)	Grade 3 or Higher n (%)
Tachycardia (GT)	12 (15)	0 (0)
Ventricular arrythmias and cardiac arrest	2 (2.2)	1 (1)
Myocardial infarction	1 (1)	1 (1)

Abbreviations: GT = grouped term, as defined in Appendix 1.
(Source: FDA analysis of ADAE dataset)

Renal Toxicity:

Increased blood creatinine of any grade was reported as AE in 3 subjects (3%); no Grade

≥3 renal toxicity was reported in subjects treated with lisocabtagene maraleucel on Study BCM-003.

Hospitalization

Seventy (79%) of lisocabtagene maraleucel-treated subjects received CAR-T infusion in an inpatient setting. The median duration of hospitalization for lisocabtagene maraleucel administration was 14 days (range: 2 to 100 days). The median total duration of all hospitalizations in these subjects was 15 (range: 2 to 196 days). Among the subjects who received inpatient lisocabtagene maraleucel infusion, three (3%) subjects were hospitalized due to an AE and four subjects were admitted to the ICU for a median of 3.0 days (range: 2 to 29 days).

Nineteen subjects (21%) received lisocabtagene maraleucel in the outpatient setting, and 13 were hospitalized after lisocabtagene maraleucel administration. Four subjects were hospitalized within 4 days after lisocabtagene maraleucel administration; the median time from lisocabtagene maraleucel administration to first hospitalization in subjects who were hospitalized was 9.0 days (range: 2 to 161 days). The median duration of hospitalization after lisocabtagene maraleucel administration was 9.0 days (range: 4 to 33 days). The initial hospitalization was most often due to an adverse event (10 subjects). None of these subjects had an ICU stay.

6.1.12.6 Clinical Test Results

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for replication competent retrovirus (RCR) and antibodies to lisocabtagene maraleucel.

Toxicity grading was based on CTCAE version 4.03 criteria. The most common Grade 3 and 4 laboratory hematologic and non-hematologic abnormalities that occurred in ≥10% of subjects are depicted in Table 34 and Table 35.

Note that post-lisocabtagene maraleucel lab toxicity includes lab toxicities observed on or after the lisocabtagene maraleucel infusion date. While baseline lab assessment is defined as the last value taken on or prior to the first dose of conditioning chemotherapy.

Table 34: Grade 3 or 4 Hematologic Laboratory Abnormalities by Lab Shift (≥ 10%) in Study BCM-003 (N=88 Evaluable).

Laboratory Abnormality	Grade 3 or 4 n (%)
Lymphocyte count decreased	86 (98)
White blood cell decreased	80 (92)
Neutrophil count decreased	78 (89)
Platelet count decreased	42 (48)
Anemia	28 (32)

(Source: Adapted from response to FDA IR dated 26APR2022 Table 20.T.5.2.1.1 page 28)

Reviewer comment(s)

The hematologic laboratory abnormalities are expected and consistent with results observed in subjects who have received lymphodepletion chemotherapy.

Table 35: Grade ≥ 3 Non-Hematologic Laboratory Abnormalities (≥ 10%) in Study BCM-003 (N = 89).

Laboratory Test	All grade n (%)	Grade 3-4 n (%)
Alanine aminotransferase increased	34 (38)	1 (1)
Aspartate aminotransferase increased	25 (28)	0
Hypophosphatemia	20 (23)	6 (7)
Hypokalemia	19 (21)	1 (1)
Hypermagnesemia	17 (19)	0
Hypoalbuminemia	17 (19)	0
Hyponatremia	17 (19)	3 (3)

(Source: Adapted from response to FDA IR dated 26APR2022 Table 20.T.5.2.2.1 page 32)

The most common Grade ≥3 non-hematologic abnormalities include hypophosphatemia (7%), hyponatremia (3%), ALT increased (1%), and hypokalemia (1%).

6.1.12.7 Dropouts and/or Discontinuations

Please refer to Section 6.1.11.4.

- **6.1.13 Study Summary and Conclusions**

The efficacy of lisocabtagene maraleucel was studied in BCM-003, a Phase 3, randomized, open label, multicenter study of second-line therapy of LBCL, that randomized 184 subjects in a 1:1 ratio to either a single infusion of lisocabtagene-maraleucel (preceded by lymphodepleting chemotherapy) or to standard therapy. All subjects had either primary refractory disease or relapse within 12 months of completing first-line therapy, and who were potentially eligible for autologous HSCT, and had not yet received second-line treatment. Standard therapy consisted of protocol defined, platinum-based chemoimmunotherapy for two to three cycles followed by high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT) in subjects achieving CR or PR.

The primary endpoint was event-free survival (EFS) determined by a blinded independent review committee (IRC). Key secondary endpoints were complete response (CR) rate, progression-free survival (PFS) per IRC and overall survival (OS). Altogether, 74% of the study population had primary refractory disease, 27% had early relapsed disease. The most common NHL types were de novo DLBCL (64%), high-grade B-cell lymphoma (23%), and primary mediastinal B-cell lymphoma (10%).

A total of 92 subjects were randomized to the lisocabtagene-maraleucel arm and 89 subjects (97%) received conforming lisocabtagene maraleucel. ORR per central assessment in the lisocabtagene maraleucel treated subjects was 86% (79/92) with CR rate of 66% (61/92).

A total of 92 subjects were randomized to the standard therapy arm out of whom 91 (99%) received any protocol specified chemoimmunotherapy; 48% (out of 92) of the subjects who received any protocol-specified therapy responded per central assessment with a CR rate of 39%; and 47% (42 out of 92) of the treated subjects underwent HSCT. The reasons for not proceeding with HSCT include lack of efficacy, disease progression, physician decision, death, and AE.

There is a clear difference in the proportion of subjects receiving definitive treatment between the two arms; 97% of subjects in the lisocabtagene maraleucel arm received the CAR-T therapy, whereas 47% of subjects in the standard therapy arm underwent HSCT.

There are two reasons that might explain the difference in receiving the definitive therapy 1) lisocabtagene maraleucel is a single CAR-T dose infusion versus multiple cycles of chemotherapy and 2) the refractoriness of the enrolled population.

EFS was significantly improved for lisocabtagene maraleucel compared to the standard therapy arm with a stratified HR of 0.34 (95% CI:0.22, 0.51) and a p- value <0.0001. The median EFS in the lisocabtagene maraleucel arm was 10.1 months (95% CI: 6.1, NR) compared to 2.3 months (95% CI: 2.2, 4.3) in the standard therapy arm. The estimated 24-month EFS in the lisocabtagene maraleucel arm was 38% (95% CI: 21.3, 54.8) vs. 18% (95% CI: 7.4, 31.9) in standard therapy arm. The most common EFS event in both the lisocabtagene maraleucel arm and standard therapy arm was disease progression (28% and 42%). Failure to achieve CR or PR by 9 weeks post-randomization was the second most common EFS in the standard therapy arm 19% vs 4% in the lisocabtagene maraleucel arm.

The IRC-assessed CR rate was higher at 66% (95% CI: 56, 76) in the lisocabtagene maraleucel arm compared to 39% (95% CI: 29, 50) in the standard therapy (p-value of <0.0001). The difference in CR between the two treatment arms was 27% (95% CI: 12, 41) with a one-sided p-value <0.0001. The median PFS also favored the lisocabtagene-maraleucel arm (14.8 months; 95% CI: 6.6, NR) compared to the standard therapy arm (5.7 months; 95% CI: 3.9, 9.4). The interim OS analysis was not statistically significant. OS tended to favor lisocabtagene maraleucel, with a HR of 0.509 (95% CI: 0.258, 1.004), one-sided p-value = 0.0257.

Study BCM-003 design was limited to assess superiority of lisocabtagene-maraleucel compared to HSCT in subjects with chemo sensitive relapse who were candidates to undergo HSCT. Subjects were randomized in advance to the two treatments arms, bridging therapy with any of the standard therapy platin based chemotherapy was allowed in the lisocabtagene maraleucel arm. Almost half of the patients in the standard therapy arm responded to the chemotherapy and underwent HSCT.

Safety analysis: The safety population for the lisocabtagene maraleucel arm included 89 subjects that received conformal product treated with one dose.

In summary:

- The most common non-laboratory adverse reactions (incidence ≥ 20%) included fever, cytokine release syndrome (CRS), musculoskeletal pain, headache, fatigue, nausea, constipation, dizziness.
- The most comment Grade 3 or 4 laboratory abnormalities (incidence ≥10%) included: lymphopenia (98%), leukopenia (92%), neutropenia (89%), thrombocytopenia (48%), AST increased (38%), anemia (32%), hypophosphatemia (23%), hypokalemia (21%), hypermagnesemia (19%), hypoalbuminemia (19%), hyponatremia (19%).
- Grade 3 or higher adverse reactions occurred in 81 (91%) subjects.
- SAEs occurred in 34 (38%) subjects and included CRS, febrile neutropenia, fever, sepsis, viral infection, neutropenia, thrombocytopenia, encephalopathy, and pulmonary embolism.
- Two subjects had fatal adverse reactions: one with failure to thrive in the context of disease relapse not considered study drug related and a second subject died of COVID during the treatment period. Four subjects died of COVID-19 during the post-treatment follow-up phase.

- Most common Grade 3 or higher AESIs included: prolonged cytopenias (40 subjects; 45%), febrile neutropenia (9 subjects; 10%), infections (7 subjects; 6%) neurologic toxicities (7 subjects; 8%), and CRS (1 subject; 1%).
- Any grade CRS occurred in 44 (49%) subjects, and any grade neurologic toxicity occurred in 18 (20%) subjects.

No new safety signals were identified in this submission. CRS and neurologic toxicity associated with lisocabtagene maraleucel are serious, life-threatening and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks.

Due to the lack of long-term safety data in the sBLA, a postmarketing long-term follow-up registry study to fulfil the 017001 post-marketing requirement will enroll 1500 DLBCL patients. Follow up of patients for 15 years in this study will provide long-term safety data.

To enhance safety, the following measures should be followed:

• The product label includes a boxed warning for CRS and NT, and the warnings and precautions section conveys the treatment algorithm for CRS and NT management.

• Daily monitoring following lisocabtagene maraleucel infusion for 7 days.

• REMS with ETASU.

In summary, BCM-003 represents an adequate and well-controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval.

The review team recommends granting regular approval for lisocabtagene maraleucel for the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy.

Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system lymphoma

6.2. Study 017006 (PILOT)

Study identification codes

- IND # 016506
- ClinicalTrials.gov identifier NCT 03483103.

Study Title:

A Phase 2 Study of Lisocabtagene Maraleucel as Second-Line Therapy in Adult Patients with Aggressive B-Cell NHL (TRANSCEND-PILOT-017006).

- **6.2.1 Objectives**

Study 017006 is a single-arm, open-label, multicenter, Phase 2 study to determine the antitumor activity, PK, and safety of lisocabtagene maraleucel in subjects who were refractory or relapsed to frontline immunochemotherapy for LBCL and are ineligible for high-dose therapy and HSCT due to age or comorbidities.

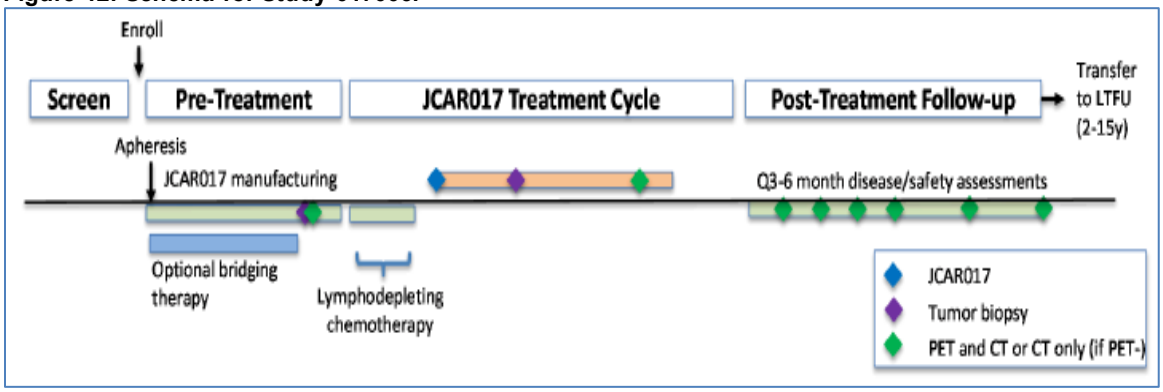
Primary objective: Antitumor activity

Secondary objective: Durability of response and safety

- **6.2.2 Design Overview**

Figure 12 shows the study schema.

Figure 12: Schema for Study 017006.



(Source: Figure 6.1-1 of the Study 017006 Interim CSR)

Pre-treatment phase:

- Upon enrollment, leukapheresis was performed to enable manufacturing of lisocabtagene maraleucel.
- A baseline tumor biopsy (either a historical sample, or a fresh tumor sample) was obtained.
- While lisocabtagene maraleucel was being manufactured, subjects were allowed to receive bridging chemotherapy, such as low-dose chemotherapy or one cycle of non-curative standard antitumor therapy.

Treatment phase:

Upon successful manufacturing of the product, subjects entered the treatment phase, which included:

- Lymphodepletion (LD) with fludarabine and cyclophosphamide.
- Lisocabtagene maraleucel by intravenous infusion 2 to 7 days following

completion of LD.

Post-treatment phase:

Subjects received post-treatment follow-up for 2 years to assess safety, PK and biomarkers, disease status, HRQoL, and survival.

Long-term follow-up (LTFU) phase:

After completion of 2 years of assessments on the study, long-term follow-up (LTFU) for survival, long-term toxicity, and viral vector safety were continued under a separate protocol for up to 15 years.

Dose Selection:

The target dose of 100 × 10^6 CAR+ T cells administered in Study 017006 was selected based on data from the Phase 1 Study, 017001.

- **6.2.3 Population**

Inclusion Criteria:

1. Age ≥ 18 years
2. Histologic confirmation of relapsed or refractory (R/R) aggressive B-cell NHL of the following histologies: DLBCL NOS (de novo or transformed follicular lymphoma [tFL]), HGBL with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple hit lymphoma [DHL/THL]) or FL Grade 3B per WHO 2016 classification.
3. Failure of first-line chemoimmunotherapy containing an anthracycline and a CD20-targeted agent, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).
4. Subjects must be deemed ineligible for both high-dose chemotherapy and HSCT while also having adequate organ function for CAR T cell treatment.
    a) Transplant ineligibility criteria (must meet at least one):
        1. Age ≥ 70 years.
        2. ECOG PS = 2.
        3. Impaired pulmonary function: diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60% adjusted for gender-specific hemoglobin concentration.
        4. Impaired cardiac function: LVEF < 50% (but ≥ 40%) assessed within 4 weeks
        5. Impaired renal function: creatinine clearance < 60 mL/min (but >30).
        6. Impaired hepatic function: AST or ALT > 2 × ULN.
    b) Adequate organ function criteria (must meet all):
        1) SaO2 ≥ 92% on room air AND CTCAE Grade ≤1 dyspnea.
        2) LVEF ≥ 40%.
        3) creatinine clearance > 30 mL/min.
        4) AST/ALT ≤ 5 × ULN.
        5) having adequate bone marrow function to receive lymphodepleting chemotherapy.
        6) Total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver).
5. PET-positive disease according to the Lugano classification.

6. ECOG PS of 0, 1, or 2.

Reviewer comment(s)

- *These subjects would be ineligible for BCM-003. The data derived from this single-arm study are the basis for the indication involving subjects with primary refractory LBCL or first relapse who are ineligible for HSCT due comorbidities or age. Transplant criteria vary by institution, and not all of the study criteria for transplant ineligibility would necessarily preclude HSCT at some institutions; in particular, the age criterion is not necessarily prohibitive. Nevertheless, the criteria are reasonable.*
- *It is important to note the strict selection criteria for this study. Although it is for a "transplant ineligible" population, subjects must still be fit enough to receive lymphodepleting chemotherapy and CAR-T therapy. The narrow window for some of the key organ function criteria is notable: for example,*
    - *a patient ineligible for HSCT due to cardiac dysfunction, with LVEF < 50%, must still have an LVEF ≥40%*
    - *a patient ineligible for HSCT due to performance status must still have an ECOG PS of 2*
    - *similarly narrow windows of eligibility are present for other organ function requirements such as pulmonary and hepatic function.*

  In order to promote the safe use of this regimen in the intended population, the requirement that transplant-ineligible patients still be fit for CAR-T therapy is important to describe in labeling and has been clearly communicated at the start of Section 14.

Exclusion Criteria:

1. Subjects with central nervous system (CNS)-only involvement by malignancy (subjects with secondary CNS involvement are allowed)
2. History of another primary malignancy that has not been in remission for at least 2 years.
3. Previous treatment with CD19-targeted therapy, except prior lisocabtagene maraleucel treatment in this protocol for subjects receiving retreatment.
4. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis.
5. Active hepatitis B, hepatitis C, or HIV infection at the time of screening.
6. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection.
7. History of life-threatening heart disease within 6 months.
8. Significant CNS pathology such as epilepsy, seizure, aphasia, stroke, dementia, Parkinson's disease, cerebellar disease, etc.

- **6.2.4 Study Treatments or Agents Mandated by the Protocol**

Lisocabtagene maraleucel

The investigational product (lisocabtagene maraleucel) is comprised of autologous CD8+ and CD4+ T cells that express a CD19-specific chimeric antigen receptor (CAR). lisocabtagene maraleucel is provided as 2 individually formulated CD8+ and CD4+ T cell frozen cell suspensions in media containing dimethyl sulfoxide (DMSO) for direct IV administration in equal CAR T-cell quantities into the subject. lisocabtagene maraleucel was administered at a total dose of 100×10^6 CAR+ T cells (50×10^6 CD8+ CAR+ T cells

and 50×10^6 CD4+ CAR+ T cells).

Lymphodepleting (LD) chemotherapy

LD was to be completed 2 to 7 days before the administration of lisocabtagene maraleucel and was compromised of the combination of two drugs:

1. Fludarabine (30 mg/m2/day for 3 days).
2. Cyclophosphamide (300 mg/m2/day for 3 days).

- **6.2.5 Directions for Use**

- Each lisocabtagene maraleucel infusion consists of CD8+ CAR+ T cells and CD4+ CAR+ T cells that must be administered separately.
- The dose of CD8+ suspension cells must be administered first, immediately followed by the administration of the CD4+ T cells.
- Each T-cell suspension (CD8+ cells or CD4+ cells) must be thawed and administered into the subject within 2 hours from removal from shipping container.
- The subject must be continuously monitored during each IV administration.

- **6.2.6 Sites and Centers**

Study 017006 was conducted at 23 sites in one country (US).

- **6.2.7 Surveillance/Monitoring**

Two study oversight committees were involved in the conduct of Study 017006:

a) Data Safety Monitoring Board (DSMB)
Prior to the start of Study 017006, an independent DSMB was established under a dedicated charter specifically developed for safety oversight of sponsored CD19 CAR T-cell studies.
b) Independent Review Committee (IRC)
The IRC was established to review disease response assessments during the study and progression status.

Schedule of evaluations

This study has three parts: pre-treatment, treatment, and post-treatment.

Pre-treatment:

- Screening, leukapheresis, and pre-treatment evaluation begins with assessing subject eligibility for study enrollment.
- If eligible, the subject will undergo leukapheresis as soon as possible, followed by pre-treatment evaluation which includes: History, physical examination with routine neurological exam, ECOG PS assessment, 12 lead electrocardiogram, mini mental status examination (MMSE), local laboratory assessments (pregnancy test, chemistries, CBC with differential, inflammatory markers, and immunoglobulins), CT scan performed at study site (must be within 6 weeks and no intervening anticancer therapy), PET scan performed at the study site (must be done within 6 weeks of the start of lymphodepleting chemotherapy, and must be done after any intervening anticancer therapy), fresh tumor biopsy (if adequate tissue is available from a previous archived tumor biopsy that was performed since the last relapse or since determination of refractory disease, a tumor biopsy will not be required; for subjects with an accessible

tumor, a biopsy must be repeated after any intervening anticancer therapy), Lumbar puncture for cerebrospinal fluid (CSF) assessment (required for subjects with suspected or confirmed CNS involvement only), HRQoL questionnaires (must be repeated after any intervening anticancer therapy).
- If needed, subjects may receive treatment between leukapheresis and lymphodepletion.

Treatment:

- All subjects receive 3 days of Fludarabine/Cyclophosphamide. lymphodepleting chemotherapy 2-7 days prior to lisocabtagene maraleucel.
- Lymphodepleting chemotherapy will be withheld if calculated creatinine clearance is $\leq$ 30 mL/min.
- Lisocabtagene maraleucel infusion will be delayed if the subject meets any of the following criteria: onset of fever ≥ 38°C/100.4°F that is not related to underlying disease, presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%, cardiac arrhythmia not controlled with medical management, hypotension requiring vasopressor support, new-onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3, taking any of the protocol prohibited medications

Post-treatment:

- Subjects were assessed for response at approximately Day 29.
- Subjects were assessed for safety twice weekly for the first 2 weeks, then twice weekly for the next 2 weeks after lisocabtagene maraleucel infusion. This immediate post-treatment assessment period included physical examination, vital signs, ECG, MMSE, ECOG PS assessment, and laboratory evaluations (CBC and differential, coagulation, chemistries, and inflammatory markers)
- Post-treatment follow-up included safety and efficacy evaluation at approximately 1, 2, 3, 6, 12, 18, and 24 months after receiving lisocabtagene maraleucel. The Month 24 visit was the end of study (EOS) visit. Each visit included: physical examination, vital signs, MMSE, ECOG PS assessment, Clinical laboratory evaluations, and HRQoL questionnaires.
- Day 29, Months 3, 6, 9, 12, 15, 18, 24 visits included PET scan, CT/MRI scan (not done if disease progression or new therapy started), CSF assessment (done if suspected or confirmed CNS involvement).
- Immunoglobulins: performed on Weeks 2,3,4. Might be performed on Months 2, 3, 6, 9, 12, 15, 18, 24 (Not required if B-cell recovery documented without recent administration of IVIG).
- Research blood samples were performed per schedule (Immunogenicity, CAR T subset expansion and persistence by flow cytometry, PK by qPCR-mediated testing for CAR T cell transgene, Biomarkers).
- All adverse events (AEs) and serious adverse events (SAEs) are collected from lymphodepleting chemo to 90 days after lisocabtagene maraleucel. After Day 90, only AEs/SAEs related to lisocabtagene maraleucel and/or protocol-mandated procedures are collected.
- Concomitant Medications associated with AEs/SAEs related to protocol-

mandated procedures were collected throughout the study.
- Anticancer therapy was recorded throughout the study.
- Hospitalizations were recorded from lymphodepletion to end of study

- **6.2.8 Endpoints and Criteria for Study Success**

Primary efficacy endpoint:

- Overall response rate (ORR), defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial response (PR), as assessed by an independent review committee (IRC) based on the Lugano 2014 criteria[11].

  The BOR was defined as the best disease response recorded from the time of lisocabtagene maraleucel infusion until disease progression, end of study, the start of another anticancer therapy or lisocabtagene maraleucel retreatment. Best response was assigned according to the following order: CR, PR, stable disease (SD), progressive disease (PD), not evaluable (NE), or not done.

Secondary efficacy endpoints:

- Complete response rate (CRR).
- Durability of response (DOR).
- DOR if BOR is CR.
- Health-related quality of life (HRQoL)

Reviewer comment(s)

- *In this memo, we used two methods for response assessment of the primary endpoint:*
  A) The IRC-FDA algorithm
  B) The response assessed by IRC based on Lugano 2014 criteria.
- *The IRC-FDA algorithm was performed based on IRC assessments, per IRC charter. The IRC-FDA algorithm categorized the below four scenarios as progressive disease (PD) regardless of PET-based metabolic response at that time point:*
  1. *Complete metabolic response/partial metabolic response (CMR/PMR) on PET and disease progression on CT scan.*
  2. *Stable metabolic disease (NMR) on PET and disease progression on CT scan.*
  3. *New lesion on CT scan indicating disease progression which is not FDG avid on PET.*
  4. *Clinical (non-radiographic) PD per investigator.*

Given the similarities in outcome by IRC review and IRC-FDA review, the IRC assessment will be used for labeling.

- **6.2.9 Statistical Considerations & Statistical Analysis Plan**

Please refer to statistical review memo for details.

Statistical hypothesis:

- The analysis of the primary efficacy endpoint was performed by testing H_0: $\pi \leq 50\%$ versus H_a: $\pi > 50\%$, where π is the ORR per IRC-FDA assessment in the lisocabtagene maraleucel–treated Efficacy Analysis Set.

- The historical ORR rate of 50% was based on the Applicant's meta-analysis from 12 published studies of second-line therapy for patients with R/R aggressive LBCL.

- **6.2.10 Study Population and Disposition**

6.2.10.1 Populations Enrolled/Analyzed

Analysis populations:

- Leukapheresed Analysis Set:
  includes all subjects who signed the informed consent form and underwent leukapheresis and informs the ITT analysis.
- Lisocabtagene Maraleucel-Treated Analysis Set:
  includes all subjects who had received at least one infusion of lisocabtagene maraleucel.
- Lisocabtagene Maraleucel -Treated Efficacy Analysis Set:
  includes all subjects in the lisocabtagene maraleucel -treated Analysis Set who had PET-positive disease present before lisocabtagene maraleucel infusion.

Table 36 summarizes the analysis sets in Study 017006.

Table 36: Analysis Sets in Study 017006.

Analysis set	N (%)
Screened Set	93
Leukapheresed Analysis Set	74 (100)
BREYANZI-treated Analysis Set	61 (82)
BREYANZI-treated Efficacy Analysis Set	61 (82)

Note: *The data cut-off date for Study 017006 is May 28, 2021.*

Reviewer comment(s)

Of 74 leukapheresed subjects, 61 (82.4%) received lisocabtagene maraleucel, of whom 61 were efficacy evaluable and constituted the primary efficacy population. However, an intention-to-treat analysis of response rate, based on all 74 patients who underwent leukapheresis, is important to evaluate and report in the USPI, particularly in a patient population with comorbidities and advanced age.

6.2.10.1.1 Demographics

Table 37 illustrates the demographic information for subjects in the leukapheresed and lisocabtagene maraleucel-treated Efficacy Analysis Set, respectively.

Table 37: Demographics and Baseline Disease Characteristics in Study 017006.

Parameter	Leukapheresed set	Efficacy analysis set
Number of subjects (n)	**74**	**61**
Age (years)		
Mean (STD)	73 (6.57)	73 (6.64)
Median (min, max)	74 (53, 84)	74 (53, 84)
Sex n (%)		
Female	29 (39.2)	24 (39.3)
Male	45 (60.8)	37 (60.7)
Race n (%)		
White	64 (86.5)	54 (88.5)
Black or African American	2 (2.7)	1 (1.6)
Asian	2 (2.7)	2 (3.3)
Unknown	6 (8.1)	4 (6.6)

(Source: FDA analysis of ADSL dataset)

Reviewer comment(s)

- *Subjects' demographics in the leukapheresed- and lisocabtagene maraleucel-treated Efficacy Analysis Set were similar.*
- *The median age, 74 years (range: 53 to 84), is higher than the median age (66 years) of patients diagnosed with DLBCL in the US population and is consistent with the study population being ineligible for HDCT and HSCT due to age or comorbidities.*
- *There is underrepresentation of racial and ethnic minorities in this study population. Most of the subjects who were treated on the study were white. Race-related differences in the efficacy or safety of lisocabtagene maraleucel are expected to be minimal but are not well characterized.*
- *The representation of males and females was balanced in this study.*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 38 shows the baseline characteristics for subjects in the primary Efficacy Analysis Set.

Table 38: Baseline Characteristics in the Primary Efficacy Analysis Set in Study 017006.

Parameter	N=61
Pre-lymphodepletion ECOG PS, n (%)	
0	18 (30)
1	27 (44)
2	16 (26)
Type of B-cell NHL, n (%)	
DLBCL, NOS	31 (50)
Transformed follicular lymphoma	9 (15)
High-grade lymphoma with DLBCL histology	20 (33)
FL3B (Follicular lymphoma, Grade 3B)	1 (2)
Reported Double Hit or Triple Hit, n (%)	
Yes	20 (33)
No	36 (59)
Missing	5 (8)
Refractory or Relapsed, n (%)	
Primary refractory	32 (52)
Relapsed	29 (48)
o Relapsed <= 12 months from initial CR	o 14 (23)
o Relapsed > 12 months from initial CR	o 15 (25)
Active CNS disease at lisocabtagene maraleucel infusion	

Parameter	N=61
Yes	0
No	58 (95)
Unknown	3 (5)
Best response to first-line therapy, n (%)	
Complete Response (CR)	29 (47.5)
Partial Response (PR)	15 (24.6)
Stable Disease (SD)	4 (6.6)
Progressive Disease (PD)	13 (21.3)
Time from LBCL diagnosis to first lisocabtagene maraleucel infusion (months)	
Mean (standard deviation)	27 (36)
Median (Min, Max)	14 (2, 183)

(Source: FDA analysis of ADSL dataset)

Table 39 illustrates the baseline transplant ineligibility criteria for subjects in the lisocabtagene maraleucel- treated *Efficacy Analysis Set.*

Table 39: Transplant Ineligibility Criteria in Study 017006 (Lisocabtagene Maraleucel– Treated Analysis Set) (N=61).

Transplant Ineligibility Criteria	N (%)
Age ≥ 70 years	
n (%)	48 (79)
Screening ECOG PS =2	
n (%)	16 (26)
Screening DLCO, n (%) [a]	
≤ 60%	4 (9)
< 50%	1 (3)
≥ 50 to ≤ 60%	3 (6)
Screening LVEF (%)	
< 50%, n (%)[a]	1 (1.6)
< 45%, n (%)[a]	1 (1.6)
Screening CrCl, n (%) [a]	
< 60 mL/min	15 (24.6)
< 50 mL/min	4 (6.6)
≥ 50 to < 60 mL/min	11 (18.0)

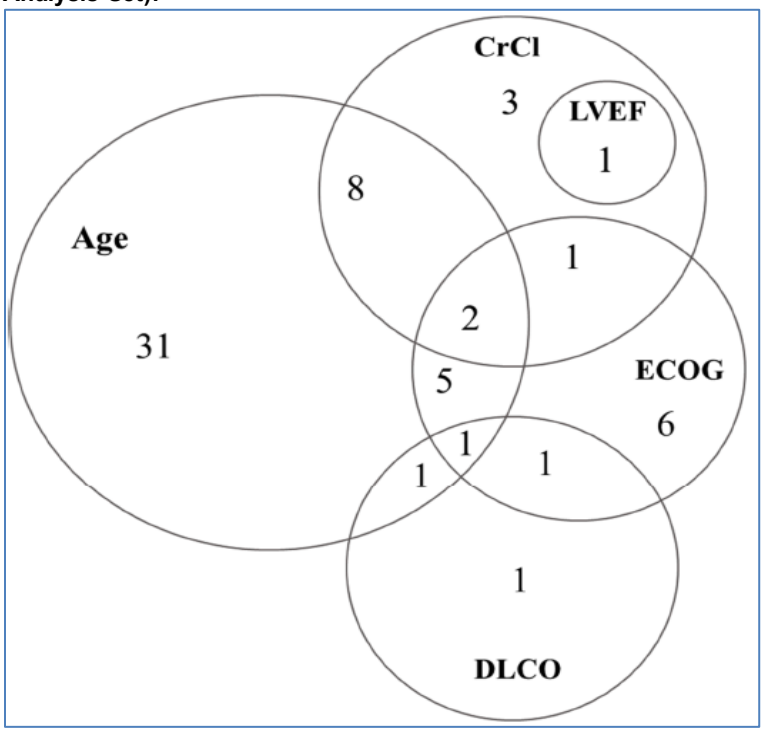
[a] Percentages are based on number of subjects with non-missing results.
(Source: clinical reviewer analysis of ADSL.xpt)

Reviewer comment(s)

The demographic and baseline disease characteristics of the Study 017006 population may not be representative of the general transplant-ineligible population with LBCL after one prior line of therapy, because of the requirement to be fit enough for LDC and CAR-T cell therapy.

Figure 13 shows the overlapping baseline transplant ineligibility criteria for subjects in the lisocabtagene maraleucel- treated Efficacy Analysis Set.

Figure 13: Transplant Ineligibility Criteria Met in Study 017006 (Lisocabtagene Maraleucel- Treated Analysis Set).



Source: Figure 8.2.1-1 of the Study 017006 CSR.

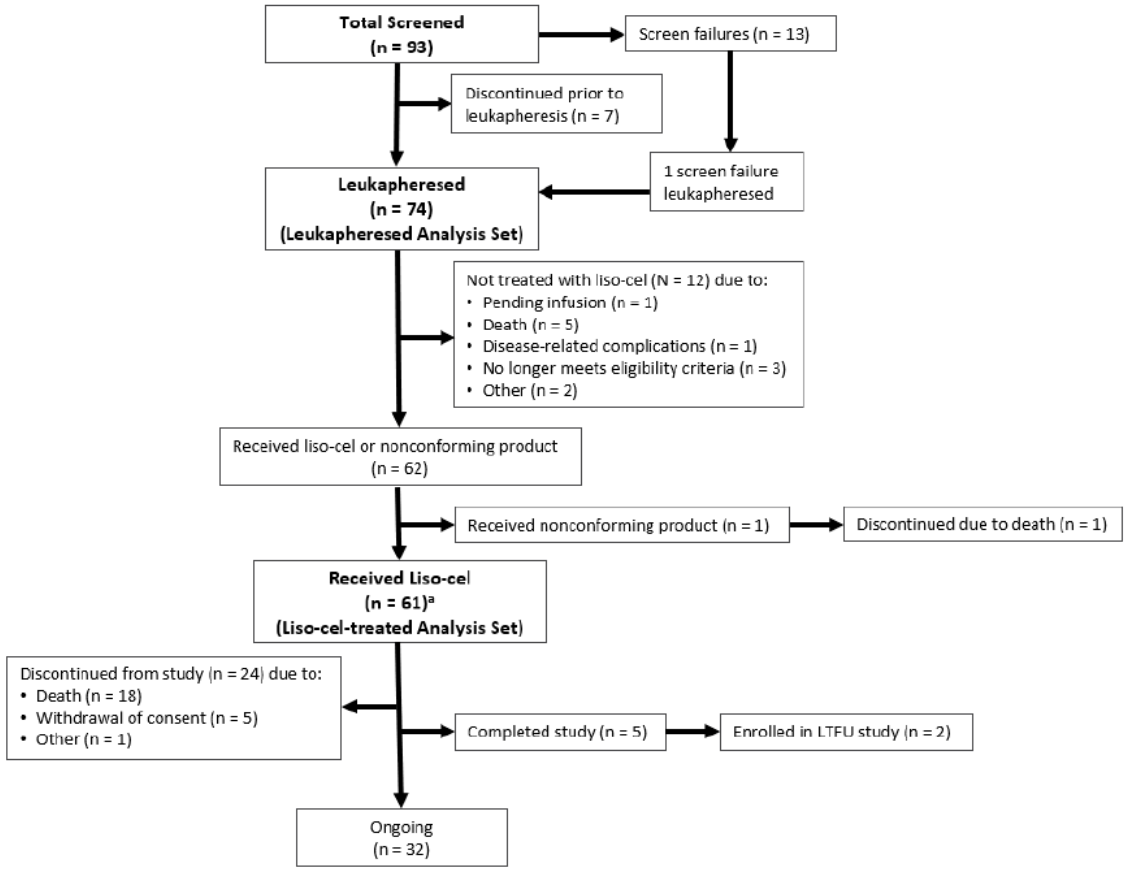
Reviewer comment(s)

- *All 61 subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set met at least one transplant ineligibility criterion as shown in Table 39 and Figure 14.*
- *Of these 61 subjects, 41 met one criterion, 17 met two criteria, and three met three criteria.*
- *Of the 31 subjects who met only the age ≥ 70 years criterion, the median age was 74 years (range: 70 to 84).*

6.2.10.1.3 Subject Disposition

The flow diagram presented in Figure 14 illustrates the subject disposition in Study 017006.

Figure 14: Subject Disposition in Study 017006.



(Source: sBLA 125714/90 clinical overview)

Reviewer comment(s)

At the time of data cutoff, May 28, 2021, out of the 61 subjects in the lisocabtagene maraleucel- treated Efficacy Analysis Set who received conforming lisocabtagene maraleucel product, 5 had completed the study, 32 had ongoing follow up, and 24 had discontinued the study. Among the 24 subjects who discontinued, the most common reason for discontinuation was death (N = 18) due to disease progression.

- **6.2.11 Efficacy Analyses**

- Primary efficacy analyses were conducted on the lisocabtagene maraleucel–treated Efficacy Analysis Set.
- In this memo, response assessment was performed as per IRC-FDA algorithm and as per IRC assessment based on Lugano 2014 criteria.

<u>Bridging Therapy:</u>

- 32/61 (52.5%) subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set received bridging therapy for disease control prior to lymphodepleting chemotherapy (LDC) while lisocabtagene maraleucel was being manufactured.
  - 21 (34.4%) received platinum-based bridging therapy and
  - 10 (16.4%) received non-platinum-based bridging therapy.
- 1/61 (1.6%) subject achieved CR after receiving bridging therapy. This subject went on to receive lisocabtagene maraleucel after disease relapse.

Lymphodepleting chemotherapy (LDC):

LDC was to be completed between 2 and 7 days prior to lisocabtagene maraleucel administration. Overall, the median time from LDC to lisocabtagene maraleucel infusion was 4 days (range: 3 to 7 days).

Lisocabtagene maraleucel:

- Conforming lisocabtagene maraleucel CD8 and CD4 drug product components were administered to 61 subjects.
- Subjects received a median CD8 dose of 49.9 × 10^6 CAR+ T cells (range: 21 to 51) and a median CD4 dose of 49.9 × 10^6 CAR+ T cells (range: 39 to 52).
- The median total dose of lisocabtagene maraleucel was 99.9 × 10^6 CAR + T cells (range: 64 to 103).
- While all subjects received the correct volume of lisocabtagene maraleucel that they were assigned, seven subjects received a lisocabtagene maraleucel dose of 64.5 to 92.2 × 10^6 CAR+ T cells, because the Applicant developed two (b) (4) methods to determine transduction frequency, one for detection of a surrogate, EGFRt (indirect), and the other for direct detection of the CD19-specific CAR. In Study 017006, the indirect CAR detection method was used in the seven subjects at the time of product release. For the remaining subjects the direct CAR detection method was used. During bridging between the two (b) (4) assays, the two methods were unexpectedly found to be discordant in the proportion of drug product lots for one or both of the CD4 and CD8 components resulting in an overestimation of transduction frequency and an administered dose of between 64.5 to 92.2 × 10^6 CAR+ T cells in these seven subjects, below the target dose of 100 × 10^6 CAR+ T cells for the study.

Reviewer comment(s)

- *Although the planned dose was 100 × 10^6 CAR+ T cells, a dose range of 90 -110 × 10^6 CAR+ T cells (100 million +/- 10%) has been assessed to be acceptable for approval given the variability in manufacturing of a biological product, and data to support efficacy at doses lower than 100 × 10^6 and safety data with doses up to 110 × 10^6.*
- *The lower limit is supported by the fact that 6/7 subjects in Study 017006 who received a lower dose (64-92 x 10^6 CAR+ T cells) achieved an objective response including three subjects achieving complete remission. Additionally, in the 3rd and later line setting, CRs were achieve with doses as low as 50 × 10^6 in Study 017001. Therefore, the proposed lower limit of the dose range 90 x 10^6 CAR+ T cells was considered acceptable by the clinical team.*
- *The upper limit of the dose that was received on Study 017006 was 103 × 10^6 CAR+ T cells. However, three dose levels ranging between 50 - 150 x 10^6 CAR+ T cells were previously investigated in Study 017001(n=268) and the upper limit of 110 x 10^6 CAR+ T cells (dose level 2) was found to be safe and effective and was approved as the upper dose limit. Therefore, the proposed upper limit of the dose range 110 x 10^6 CAR+ T cells was considered acceptable by the clinical team.*

6.2.11.1 Analyses of Primary Endpoint(s)

Table 40 shows the best overall response (BOR) per IRC-FDA algorithm and the BOR per IRC assessment for leukapheresed and lisocabtagene maraleucel- treated efficacy

populations.

Table 40: BOR per IRC-FDA vs. BOR per IRC in Study 017006.

Parameter	BOR per IRC-FDA Algorithm		BOR per IRC Assessment	
	Leukapheresed Set (N=74)	Efficacy Analysis Set (N=61)	Leukapheresed Set (N=74)	Efficacy Analysis Set (N=61)
ORR (CR+PR), n (%)	**49 (66)**	**48 (79)**	**50 (68)**	**49 (81)**
95% CI[b]	(54, 77)	(66, 88)	(56, 78)	(68, 90)
CR rate, n (%)	**34 (46)**	**33 (54)**	**34 (46)**	**33 (54)**
95% CI	(34, 58)	(41, 6)	(34, 58)	(41, 67)
PR rate, n (%)	15 (20)	15 (25)	16 (22)	16 (26)
95% CI	(12, 31)	(15, 37)	(13, 33)	(1, 3)
SD, n (%)	1 (1)	1 (2)	3 (4)	3 (5)
PD, n (%)	11 (15)	11 (18)	8 (13)	8 (1)
NE, n (%)	13 (1)	1 (2)	13 (18)	1 (2)

CI=confidence interval; NR=Not reached
[a]Per the Lugano criteria.
[b]2-sided 95% exact Clopper-Pearson confidence intervals.
(Source: FDA statistical reviewer analysis)

- The assessments based on IRC-FDA and IRC made the same BOR call in 58/61 (N =95%) of the cases.
- Most importantly, 48 subjects were determined to be responders by both IRC-FDA and IRC (33 CRs, 15 PRs) assessments.
- In 3/61(=5%) of cases, the BOR assessments based on IRC-FDA and IRC were discordant:
    - One subject who was assessed to have a BOR of PR per IRC, was assessed to have BOR of PD per FDA-IRC assessment.
    - Two subjects who were assessed to have a BOR of SD per IRC, were assessed to have BOR of PD per FDA-IRC assessment.

Time to Response

In the lisocabtagene maraleucel- treated Efficacy Analysis Set, the median time to first CR or PR based on IRC assessment was 0.95 months (range 0.8 to 3.0 months). The median time to first CR was 0.95 months (range 0.8 to 6.9 months).

Reviewer comment(s)

1) *The primary efficacy analysis of Study 017006 succeeded in reaching its primary endpoint of a clinically meaningful magnitude of an ORR (CR+PR) based on IRC-FDA assessment. As displayed in Table 40, 48/61 (79%) subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set (n= 61) had a BOR of CR or PR, as determined by IRC-FDA algorithm. The lower limit of the 95% exact Clopper-Pearson confidence interval for ORR was 66.3% which is well above the pre-specified null hypothesis rate of 50%.*

2) *The ORR assessments based on IRC-FDA and IRC was concordant in 48/49 (98%) of responders (33 CRs, 15 PRs) The single exception was one subject, who was assessed to be a partial responder (PR) by the IRC but was assessed to have progressive disease (PD) per FDA-IRC assessment.*

The concordance and negligible difference between the IRC-FDA assessment and IRC

assessment, was the basis for the decision to use the IRC assessment in labeling.

6.2.11.2 Analyses of Secondary Endpoints

A. Complete response rate (CRR)

Complete response rate is summarized in Table 40. Among the 48 responders, 33 (54%) had a best response of CR based on IRC-FDA and IRC assessments.

Reviewer comment(s)

The secondary efficacy analysis of Study 017006 succeeded in reaching a clinically meaningful magnitude of CRR.

B. Durability of Response

Table 41 summarizes DOR in the overall Efficacy Analysis Set per IRC- FDA and IRC assessments.

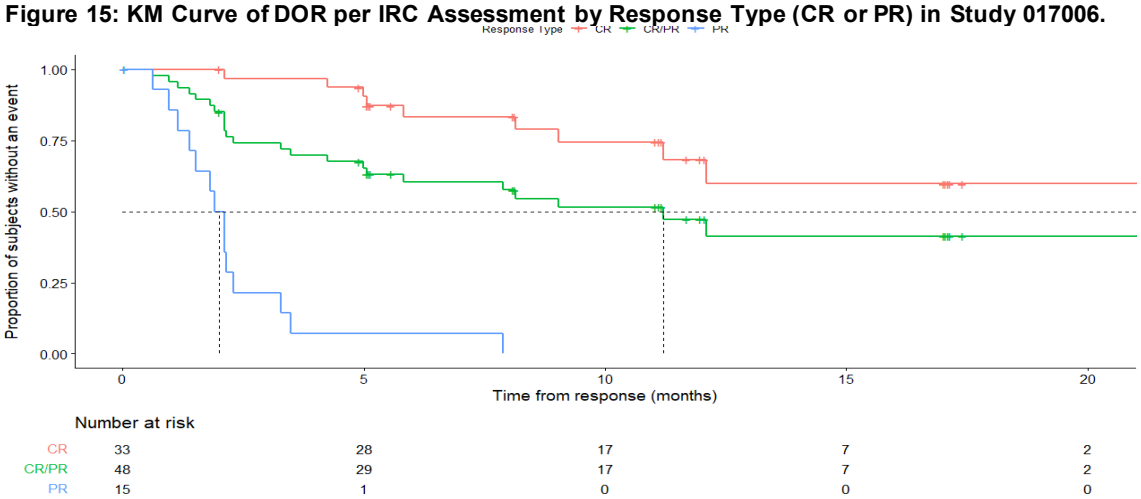
Table 41: DOR Results per IRC-FDA and IRC Assessment in Study 017006.

	IRC-FDA algorithm	IRC assessment
Number of subjects achieved CR or PR	N = 48	N = 49
	n (%)	n (%)
Number of events, n (%)	24 (50)	22 (45)
Progression	23 (48)	21 (43)
Death	1 (2)	1 (2)
Censored, n (%)	24 (50)	27 (55)
Ongoing	22 (46)	22 (45)
Completed the Study	1 (2)	1 (2)
Discontinued the study	1 (2)	1 (2)
Received a new anticancer therapy	0	3 (6)
DOR (months)		
Estimated Median	11.20	11.20
95% CI	(4.99, NR)	(5.06, NR)
Follow-up (months)		
Estimated Median	11.2	11.2
95% CI	(11, 17)	(8, 16)
Kaplan-Meier estimate of DOR rate (%) at:		
6 months (95% CI)	60 (46, 73)	62 (46, 74)
12 months (95% CI)	47 (31, 62)	49 (31, 64)

(Source: FDA statistical reviewer's analysis)

As shown in Figure 15 and Table 42, complete responders tended to have substantially longer DOR than partial responders. The estimated median DOR for the partial responders was 2.0 months (95% CI: 1.15, 2.3), while the estimated median DOR was 21.7 months for complete responders (95% CI: 11.2, NR).

Figure 15: KM Curve of DOR per IRC Assessment by Response Type (CR or PR) in Study 017006.



(Source: FDA statistical reviewer's analysis)

Table 42: Duration of Response by BOR per IRC in Study 017006.

Parameter	CR	PR
Subjects Achieved CR or PR, n	N=33	N=16
Progression or Death, n (%) [a]	9 (27%)	13 (81%)
Progression	9 (27%)	12 (75%)
Death	0	1 (6%)
Censored, n (%) [a]	24 (73%)	3 (19%)
Received a new anticancer therapy	1 (3%)	2 (13%)
Retreated with study product	0	0
Discontinued the study	1 (3%)	0
Completed the study	1 (3%)	0
Ongoing	21 (64%)	1 (6%)
DOR Estimates		
Median, (95% CI) [b]	NR (11.20-NR)	2.10 (1.38-2.30)
Min, Max	2.0, 22.8	0.0, 7.9
DOR rate at:		
6 months (95% CI)	83 (64-93)	8 (0.5-31)
12 months (95% CI)	68 (45-83)	- (-)

[a] *Denominator is number of subjects in the Efficacy Analysis Set who achieved CR or PR.*
[b] *Kaplan-Meier (KM) method is used to obtain 2-sided 95% confidence intervals.*
(Source: adapted from FDA statistical reviewer's analysis)

Reviewer comment(s)

- *The basis of FDA's conclusion of substantial evidence of effectiveness in subjects with LBCL who received lisocabtagene maraleucel after failure of first-line therapy and who are ineligible for HSCT due to age or comorbidities is the magnitude of efficacy primarily driven by durable CR rate.*
- *The finding that durable remissions tend to be restricted to patients who achieve*

CR is consistent across LBCL studies of lisocabtagene maraleucel, as well as LBCL studies of other approved CAR-T products. Given the generally short-lived remissions in patients who achieve a best overall response of PR, the basis of the efficacy determination for regulatory purposes is CR rate with durability, rather than ORR.

C. Patient-Reported Outcomes (PRO)

Health-related quality of life (HRQoL) was assessed as a secondary endpoint based on changes in the European Organization for Research and Treatment of Cancer (EORTC) QLQ- C30, the FACT-Lym subscale, and the EuroQol instrument EQ-5D-5L. Numbers of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization were also assessed.

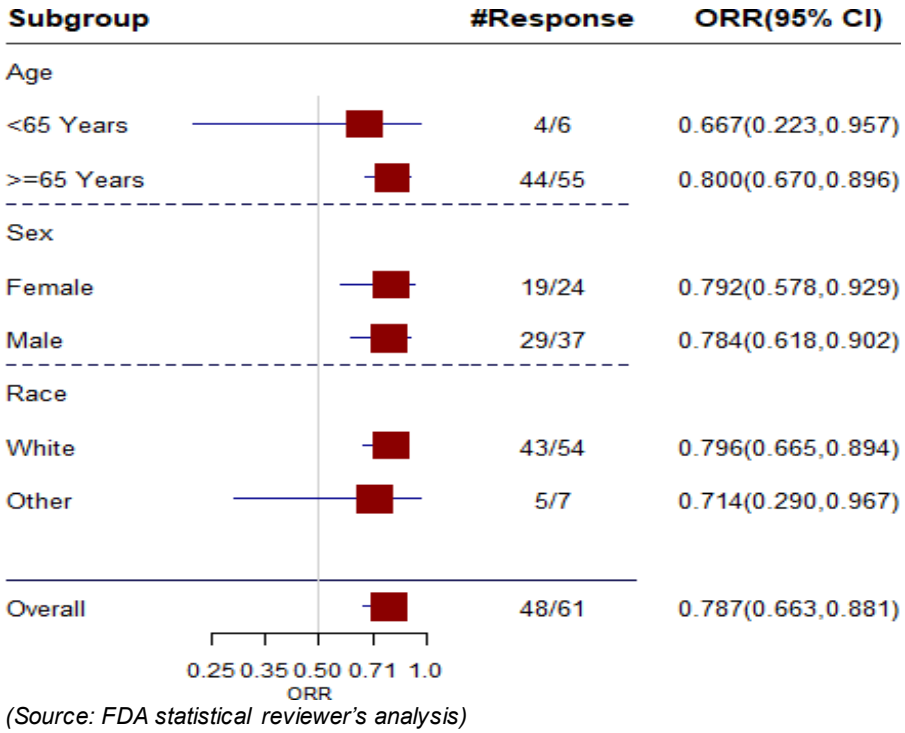
Reviewer comment(s)

The Applicant did not seek a labeling claim based on HRQoL data and these data were not incorporated in the PI. The data were not evaluated as part of the application review, given the limitations of HRQoL assessments in uncontrolled, open-label trials. Hence, the clinical reviewer did not perform any assessment to inform safety/efficacy based on PRO endpoints.

6.2.11.3 Subpopulation Analyses

Figure 16 shows the forest plot of ORR in the lisocabtagene maraleucel-treated Efficacy Analysis Set by age group, sex and race.

Figure 16: Forest Plot of ORR by Subgroups in Study 017006.



(Source: FDA statistical reviewer's analysis)

Results of ORR appear to be generally consistent across subgroups. The lower limit of 95% exact Clopper-Pearson confidence interval for ORR is above the null hypothesis rate

of 50% for most subgroups. There were too few patients aged < 65 years and with race other than White to permit conclusions.

Table 43 shows further exploratory subgroup analyses of age in relation to response. The magnitude of the treatment effect was consistent across these subgroups.

Table 43: Age Subgroups in Study 017006.

Efficacy Subgroup	ORR % (95% CI)	CRR % (95% CI)
Age ≥ 75 n = 28	86% (67 to 96)	50% (31 to 69)
Age < 75 n = 33	76% (58 to 89)	58% (39 to 75)
Age ≥ 70 n = 48	83% (70 to 93)	56% (41 to 71)
Age < 70 n = 13	69% (39 to 91)	46% (19 to 75)

Source: Table 3.3.2-2 of the SCE

Table 44 shows exploratory subgroup analyses of response to first-line systemic therapy in relation to response to lisocabtagene maraleucel.

Table 44: Subgroups Pertaining to Response to Prior Line of Therapy in Study 017006.

Efficacy Subgroup	ORR % (95% CI)	CRR % (95% CI)
Primary Refractory (PD, SD, PR or CR <3 months to 1L therapy) n = 35	74% (57, 88)	46% (29, 63)
Relapsed (CR ≥ 3 months and ≤ 12 months) n = 11	73% (39, 94)	46% (17, 77)
Relapsed > 12 months (CR > 12 months to 1L therapy) n = 15	100% (78, 100)	80% (52, 96)

Source: Table 3.3.1-2 of the SCE

Reviewer comment(s)

- *The magnitude of the treatment effect was consistent across key subgroups, including refractory vs. relapsed status after first-line therapy.*
- *Study 017006, unlike Study BCM-003, also enrolled subjects who relapsed > 12 months after a CR to first-line therapy. In this subgroup, which included 15 (25%) subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set, consistently positive clinical results were also observed across the range of efficacy endpoints.*

6.2.11.4 Dropouts and/or Discontinuations

Table 45 shows subject dropouts and discontinuation of Study 017006.

Table 45: Subject Dropouts and Discontinuation of Study 017006.

Study Status	Total (N=61) n (%)
Discontinued from study	24 (39.3)
• Adverse event	0
• Death ○ COVID-19 related ○ sepsis	18 (29.5) ○ 2 (3.3) ○ 1 (1.6)
• Other	1 (1.6)
• Subject withdrew consent ○ COVID-19 related ○ Subjects received retreatment ○ Enrolled in the long-term follow-up study	5 (8.2) ○ 1 (1.6) ○ 2 (3.3) ○ 2 (3.3)

(Source: Modified from Study 017006 Interim CSR, Table 7.1.1-1)

Reviewer comment(s)

Lisocabtagene maraleucel was administered as a single dose in all subjects and follow-up continued for subjects regardless of AEs. Hence, there are no concerns that study dropouts or discontinuations might have caused bias and affected the efficacy results of the study.

6.2.11.5 Exploratory and Post Hoc Analyses: Not applicable.

- **6.2.12 Safety Analyses**

6.2.12.1 Methods

The key materials used for the safety review included:

- Applicant submissions in response to the review team's information requests
- Proposed labeling for lisocabtagene maraleucel
- Published literature
- Prior regulatory history
- The clinical review of safety was primarily based upon analysis of 61 subjects in the lisocabtagene maraleucel-treated Efficacy Analysis set at the primary data cutoff of May 28, 2021. The lisocabtagene maraleucel analysis datasets (ADAM datasets) were used for the safety analysis. Analyses by the clinical reviewer for safety were performed using JMP 16. All narratives and relevant case report forms (CRFs) were reviewed for all serious adverse events (SAEs) and deaths that occurred in the primary safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0, and AE severity was graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) severity was graded as a syndrome according to a modification of the 2014 Lee criteria grading system. The modification of the Lee criteria is that neurologic AEs were not taken into account in CRS grading of organ toxicity since neurologic toxicity is now considered a distinct entity. Some AEs are presented throughout this review as grouped terms as defined by the review team. The complete list of FDA's grouped terms is presented in Appendix 1. Unless otherwise specified, all analyses and tables were generated by the FDA clinical reviewer and/or the safety review team.

- The safety analysis set included all subjects treated with one dose of conforming lisocabtagene maraleucel product. All AEs were collected from the start of leukapheresis until 90 days after lisocabtagene maraleucel infusion.
- Serious adverse events (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, resulted in persistent or significant disability, resulted in congenital anomaly or birth defect, or resulted in any other medically important serious event. SAEs were collected from the time of screening.
- Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring or worsening on or after the randomization and within 90 days after the infusion of lisocabtagene maraleucel or start of new antineoplastic therapy, whichever occurs first as those AE made known to the investigator at any time thereafter that are suspected of being related to study treatment of lisocabtagene maraleucel administration through and including 90 days. The adverse event reporting periods with the data collected during these periods were mapped as follows: 1) from randomization to LD chemotherapy 2) from LD chemotherapy to lisocabtagene maraleucel infusion (LDC) 3) lisocabtagene maraleucel first infusion to and including 90 days (TEAE).
- The following AEs were to be reported as SAEs from time of lymphodepleting chemotherapy: secondary malignancies, new onset or exacerbation of pre-existing-neurologic, rheumatologic or autoimmune disorder, new onset of hematologic disorder and rare and unexpected disorders with an unknown etiology e.g. Guillain-Barre syndrome.
- All summaries of safety data were conducted using lisocabtagene maraleucel-treated analysis Set. AEs were analyzed with a focus on TEAEs, defined as any AE that started on the day of lisocabtagene maraleucel infusion through (and including) 90 days after. Any AE that occurred after the initiation of another anticancer treatment or lisocabtagene maraleucel retreatment was not considered to be a TEAE.

6.2.12.2 Overview of Adverse Events

Table 46 shows the incidence of AEs by maximum grade in the safety population (N=61 subjects) after lisocabtagene maraleucel infusion in Study 017006.

Table 46: TEAEs in ≥ 10% of Safety Population (N=61) by System Organ Class in Study 017006.

System Organ Class and Preferred Term or Grouped Preferred Term	AE (Grade 1-5) n (%)	AE (Grade 3 and higher) n (%)
Cardiac disorders		
Tachycardia	6 (10)	0
Gastrointestinal disorders		
Nausea	15 (25)	1 (2)
Diarrhea	9 (15)	0 (0)
Constipation	7 (11)	0 (0)
General disorders and administration site conditions		
Fatigue	27 (44)	1 (2)
Fever	23 (38)	1 (1.6)
Edema	12 (20)	0 (0)

System Organ Class and Preferred Term or Grouped Preferred Term	AE (Grade 1-5) n (%)	AE (Grade 3 and higher) n (%)
Immune system disorders		
Cytokine release syndrome	24 (39)	1 (2)
Infections and infestations		
Infections – pathogen unspecified	8 (13)	3 (5)
Upper Respiratory Tract Infection	8 (13)	0 (0)
Bacterial infections	6 (10)	2 (3)
Metabolism and nutrition disorders		
Decreased appetite	8 (13)	1 (2)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	14 (23)	3 (4.9)
Nervous system disorders		
Encephalopathy	16 (26)	4 (7)
Dizziness	10 (16)	1 (1.6)
Tremor	10 (16)	0 (0)
Headache	7 (11)	1 (1.6)
Psychiatric disorders		
Insomnia	7 (11)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Cough	11 (18)	0 (0)
Dyspnea	10 (16)	3 (4.9)
Vascular disorders		
Hypotension	14 (23)	1 (1.6)
Hypertension	6 (10)	3 (4.9)

(Source: FDA analysis of ADAE, ADSL datasets)

Other clinically important Grade 1-5 AEs that occurred in <10% of the subjects treated with lisocabtagene maraleucel in Study 017006 include:

- Blood and lymphatic system disorders: Febrile neutropenia (1.6%).
- Eye disorders: Vision blurred (3.3%).
- Gastrointestinal disorders: Vomiting (8%), abdominal pain (7%), gastrointestinal hemorrhage (4.9%)
- Infections and infestations: Fungal infections (5%), sepsis (3.3%), viral infections (3%).
- Nervous system disorders: Motor dysfunction (7%), aphasia (4.9%), ataxia (4.9%), peripheral neuropathy (4.9%).
- Psychiatric disorders: Delirium (3.3%).
- Renal and urinary disorders: Renal failure (7%).
- Respiratory, thoracic, and mediastinal disorders: Hypoxia (4.9%).
- Skin and subcutaneous tissue disorders: Rash (7%).
- Vascular disorders: Thrombosis (7%).

Reviewer comment(s)

- *Information requests were sent to the Applicant to verify and re-adjudicate AEs. The reviewer requested the resubmission of updated datasets (ADAE, ADSL) that reflect FDA's review and re-adjudication and FDA grouped term.*
- *No new signal was observed on Study 017006. All grade AEs occurring in 10% or more subjects in Study 017006 are consistent with those seen with other anti-CD19 CAR-T products and in other lisocabtagene maraleucel studies (017001 and BCM-003). These AEs reflect the toxicities of the investigational protocol including lymphodepletion with fludarabine and cyclophosphamide.*
- *Although the AEs are presented by SOC, some grouped terms include more than one system, e.g., encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these grouped term AEs under the SOC with most representation in the data for that AE and/or the clinically most appropriate SOC.*
- *For analyses of infection, we included the high level group terms for bacterial, fungal, and viral infection. This was reflected in the AE high level group term (HLGT) column in the JMP datasets.*
- *Febrile neutropenia is reported as a separate grouped term under blood and lymphatic disorders, because of its relevance in clinical practice. This is different from the Study 01700 analysis, where febrile neutropenia was included as infections with pathogen unspecified.*
- *Pain as a grouped term was ultimately not included in the label, since we assessed it to be too broad a category to provide meaningful information to clinicians.*

<u>Reviewer comments pertinent to the adverse drug reaction (ADR) table of the label:</u>
The table above will serve as the basis for the ADR table of the label. The laboratory abnormalities incidence will be presented in a separate table that is derived from the ADLB datasets and not from the AE datasets since the ADLB dataset is more accurate and captures more laboratory abnormalities than the ADAE dataset. The laboratory abnormalities were based on laboratory shift analysis, with the baseline assessed before lymphodepletion and not at the time of lisocabtagene maraleucel infusion.

Table 47 shows the incidence of TEAEs that occurred in ≥ 10% of the safety population (N=61 subjects) in Study 017006. The most common nonlaboratory adverse reactions (≥ 20%) were fatigue, CRS, encephalopathy, nausea, hypotension, musculoskeletal pain, and edema.

Table 47: TEAEs in ≥ 10% of Safety Population (N=61) by Preferred Term or Grouped Preferred Term in Study 017006.

TEAE by PT or FDA grouped PT	AE (Grade 1-5) n (%)	AE (Grade 3 and higher) n (%)
Fatigue	27 (44)	1 (1.6)
Cytokine release syndrome	24 (39)	1 (1.6)
Fever	23 (38)	1 (1.6)
Nausea	15 (25)	1 (1.6)
Encephalopathy	14 (23)	4 (7)
Hypotension	14 (23)	1 (1.6)
Musculoskeletal pain	14 (23)	3 (4.9)
Edema	12 (20)	0 (0)
Cough	11 (18)	0 (0%)
Dizziness	10 (16)	1 (1.6)
Dyspnea	10 (16)	3 (4.9)
Tremor	10 (16)	0 (0)
Diarrhea	9 (15)	0 (0)
Decreased appetite	8 (13)	1 (1.6)
Infections with pathogen unspecified	8 (13)	3 (4.9)
Upper respiratory tract infection	8 (13)	0 (0)
Constipation	7 (11)	0 (0)
Headache	7 (11)	1 (1.6)
Insomnia	7 (11)	0 (0)
Bacterial infection	6 (10)	2 (3.2)
Hypertension	6 (10)	3 (4.9)
Tachycardia	6 (10)	0 (0)

Source: FDA analysis of ADAE dataset

Table 48 shows the incidence of TEAEs (Grade 3 or higher) that occurred in ≥ 2% of the safety population (N=61 subjects) in Study 017006.

Table 48: Grade ≥3 TEAEs in ≥ 2% of Safety Population (N=61) by Grouped Preferred Term in Study 017006.

AE grouped term defined by FDA	Grade 3 and higher AEs n (%)
Encephalopathy	4 (7)
Dyspnea	3 (4.9)
Gastrointestinal hemorrhage	3 (4.9)
Musculoskeletal pain	3 (4.9)
Infections - pathogen unspecified	3 (4.9)
Sepsis	3 (4.9)
Bacterial infections	2 (3.3)
Thrombosis	2 (3.2)
Viral infections	2 (3.2)

(Source: FDA analysis of ADAE dataset)

6.2.12.3 Deaths

Table 49 shows the incidence and causes of deaths in the Leukapheresed Analysis Set (N=74) in Study 017006.

Table 49: Deaths in the Leukapheresed Analysis Set in Study 017006.

	Period of Death Occurrence		
Primary Cause of Death	**Deaths between leukapheresis and LDC**	**Deaths between LDC lisocabtagene maraleucel**	**Death occurred after lisocabtagene maraleucel**
	n (%)	**n (%)**	**n (%)**
Death	5 (6.8)	0	19 (25.7)
• Disease progression	3 (4.1)		15 (20.3)
• Adverse event	1 (1.4)		3 (4.1)
• Other	1 (1.4)		1 (1.4)

(Source: FDA analysis of ADAE dataset)

Reviewer comment(s)

- *The reviewer reviewed all death narratives to confirm the cause of death. Relevant datasets and CRFs were reviewed as needed to reach a conclusion on cause of death. Disease progression was considered as cause of death when supported by imaging, biopsy, autopsy, or other descriptive narratives of progression of underlying malignancy.*
- *Most of the subjects that died after lisocabtagene maraleucel infusion (15/19) died because of disease progression.*
- *Out of the three subjects who died because of adverse events, two subjects died of COVID 19 at the peak of the pandemic and one subject died of sepsis.*
- *The total number of deaths that occurred on Study 017006 was comparable to the number of deaths in other lisocabtagene maraleucel studies.*

6.2.12.4 Nonfatal Serious Adverse Events

Table 50 shows the incidence of Nonfatal Serious Adverse Events on Study 017006. Serious adverse reactions occurred in 33% of patients.

Table 50: Nonfatal Serious Adverse Events ≥ 2% on Study 017006

Parameter	N=61 n (%)
Subjects with any serious TEAE	20 (33)
Blood and lymphatic system disorders	1 (2)
Febrile neutropenia	1 (2)
Immune system disorders	8 (13)
Cytokine release syndrome	8 (13)
Nervous system disorders	1 (2)
Encephalopathy	3 (5)
Infections and infestations	5 (7)
Infections with pathogen unspecified	3 (5)
Bacterial infectious disorders	2 (3)
Psychiatric disorders	3 (5)
Confusional state	3 (5)
Respiratory, thoracic and mediastinal disorders	2 (3)
Pulmonary embolism	2 (3)

(Source: FDA analysis of ADAE dataset)

6.2.12.5 Adverse Events of Special Interest (AESIs)

Table 51 shows AESIs in 61 subjects who received lisocabtagene maraleucel under Study 017006 by FDA grouped preferred terms.

Table 51: AESIs in Subjects Who Received Lisocabtagene Maraleucel in Study 017006

TEAEs	N=61	
	Grade 1-5 n (%)	Grade ≥3 n (%)
Subjects with any CRS	24 (39)	1 (1.6)
CRS symptoms		
Fatigue	27 (44)	1 (1.6)
Fever	23 (38)	1 (1.6)
Hypotension	14 (23)	1 (1.6)
Headache	7 (11)	1 (1.6)
Tachycardia	6 (10)	0 (0)
Chills	3 (5)	0 (0)
Subjects with any neurologic toxicity (NT)	24 (39)	4 (7)
NT symptoms		
Encephalopathy	14 (23)	3 (4.9)
Dizziness	10 (16)	1 (1.6)
Tremor	10 (16)	0 (0)
Headache	7 (11)	1 (1.6)
Aphasia	3 (5)	1 (2)
Ataxia	3 (5)	0 (0)
Delirium	3 (5)	0 (0)
Peripheral neuropathy	3 (5)	0 (0)
Taste disorder	3 (5)	0 (0)
Infections	3 (5)	0 (0)
Infections – pathogen unspecified	8 (13)	3 (5%)
Bacterial infections	6 (10)	2 (3.3)
Sepsis	3 (5)	3 (5)
Fungal infections	3 (5)	0 (0)
Viral infections	2 (3)	2 (3)

TEAEs	N=61	
	Grade 1-5 n (%)	Grade ≥3 n (%)
Prolonged cytopenias	47 (77)	19 (31)
Thrombocytopenia	38 (62)	15 (25)
Anemia	30 (49)	3 (5)
Neutropenia	24 (39)	15 (25)
Hypogammaglobulinemia	4 (7)	0 (0)
Myelodysplastic syndrome (MDS)	1 (1.6)	1 (1.6)

(Source: FDA analysis of ADAE dataset)

Cytokine Release Syndrome (CRS)

Time to onset and time to resolution of CRS

- In patients receiving lisocabtagene maraleucel in Study 017006 (n=61), the median time to CRS onset was 4 days (range: 1 to 12 days) (interquartile range [IQR]) of 3, 7).
- Median Time to resolution of CRS was 4 days (range: 1 to 12 days) (interquartile range [IQR]) of 2, 5).

Reviewer comment(s)

- *Per Lee et al. 2014, clinical signs and symptoms associated with CRS may include constitutional symptoms (e.g., fever, nausea, fatigue etc.) or other organ toxicities (e.g., cardiovascular, hepatic, renal etc.).*
- *Our review strategy of finding additional subjects with CRS included identifying fever, hypotension or hypoxia between Day 0 and Day 30 in the subjects who were not flagged as having CRS. We additionally looked for subjects not flagged as having CRS but who received tocilizumab, vasopressors, intravenous fluids (IVF) or oxygen.*
- *We reviewed cytokine and laboratory data (Ferritin, C-reactive protein, IL-6 levels) for supportive evidence. Subjects who were identified to have isolated hypotension without other symptoms suggestive of CRS were not included.*
- *After reviewing all narratives and relevant CRFs and datasets, we adjudicated one additional subject as having Grade 2 CRS.*
- *In addition, CRS grading and CRS duration were reviewed, and two cases were re-adjudicated from Grade 1 to Grade 2 CRS.*

Treatment of CRS

- Treatment of CRS included tocilizumab, corticosteroids, acetaminophen, and pantoprazole.
- In addition, four subjects received oxygen supplementation while experiencing a CRS event.

Table 52 shows for the use of tocilizumab, corticosteroids, and vasopressors for the prevention and/or treatment of CRS, using the total number of subjects in the safety population as the denominator.

Table 52: Concomitant Medication Use for Treatment of CRS in the Lisocabtagene Maraleucel-Treated Analysis Set (N = 61).

Concomitant Medication	n (%)
• Tocilizumab and/or Corticosteroid	16 (26)
• Tocilizumab only	6 (10)
• Corticosteroids only	0
• Tocilizumab and Corticosteroids	10 (16)
• Vasopressor	0

(Source: FDA analysis of ADCM dataset)

Reviewer comment(s)

- *Management of CRS with tocilizumab and/or corticosteroids as shown in Table 61 is consistent with clinical practice.*
- *Overall incidence of CRS observed in Study 017006 (41%) is similar to that observed in other lisocabtagene maraleucel studies: BCM-003 (36%) and 17001 (49%).*
- *In general, the incidence of grade 3 and higher CRS was low (7%). Lower rates of severe CRS are likely due to early recognition and intervention preventing serious toxicity and end organ damage.*

Neurotoxicity (NT)

Among 61 subjects treated with lisocabtagene maraleucel, 24 (39%) experienced one or more neurologic toxicity events. Only four subjects (7%) experienced Grade 3 or higher (severe or life threatening) events. The following neurologic toxicity events occurred in ≥2% of subjects: encephalopathy, dizziness, tremors, headache, aphasia, ataxia, delirium, peripheral neuropathy, and taste disorder. See Table 51 for details regarding NT and the individual AEs that were considered part of NT.

The median time to onset of NT was 7 days (range: 1 to 63 days) (interquartile range [IQR]) of 5, 12). Median Time to resolution of NT was 6 days (range: 1 to 89 days). (Interquartile range [IQR]) of 3, 11).

Table 53 shows additional subjects FDA neurological toxicity adjucation of 6 additional subjects not previously identified by the Applicant.

Table 53: FDA Neurological Toxicity Adjudication of 6 Additional Subjects.

USUBJID	FDA Adjudication	Rationale
(b) (6)	Grade 1 NT	The subject experienced Grade 1 dizziness starting on Day 4. Dizziness is not specific for immune effector cell associated neurotoxicity syndrome (ICANS). However, it represents neurologic toxicity from study product.
(b) (6)	Grade 1 NT	The subject experienced Grade 1 dizziness starting on Day 1 with no clear alternative explanation this symptom represents CAR-T related neurotoxicity
(b) (6)	Grade 1 NT	Subject experienced dizziness started on day 22 and resolved after 2 months with no alternative explanation
(b) (6)	Grade 1 NT	Subjects started with tremors on day 11 after CAR T cell infusion and are considered CAR T related toxicity, although not part of ICANS.

USUBJID	FDA Adjudication	Rationale
(b) (6)	Grade 1 NT	Subject experienced fine motor skill dysfunction started on Day 11 and the event of hypoesthesia started on Day 24. Both events were not preexisting conditions and both events occurred after CAR T cell infusion and therefore represent CAR T cell related toxicity, but not ICANS.
(b) (6)	Grade 1 NT	The event of tremor started on day 22 following CAR T cell infusion and are considered a CAR T related neurotoxicity, but not ICANS.

Reviewer comment(s)

- *There is a discrepancy between the numbers of all grade encephalopathy between treatment emergent encephalopathy 16 (26%) and that listed under neurologic toxicity 10 (16%). This is because treatment emergent encephalopathy, includes encephalopathy from all causes e.g. general disorder, medications, hepatic encephalopathy etc. while that described under neurologic toxicity is encephalopathy attributed to lisocabtagene maraleucel neurotoxicity*
- *The Applicant identified 18 (30%) subjects with neurologic toxicity. After reviewing all narratives and relevant CRFs and datasets, we adjudicated additional six subjects as having Grade 1 neurologic toxicity the details for whom are provided in Table 53. Any grade neurologic toxicity increased to 24 subjects (39%).*
- *Although some symptoms like tremor, headache, dizziness etc. may either be less specific for immune effector cell associated neurotoxicity syndrome (ICANS) or not require intervention if they occur in insolation, they nevertheless represent neurologic toxicity from study product and were flagged as such. We also took into consideration the timing of symptoms post study product infusion, clustering of multiple symptoms during a given time frame or sequential occurrence, and alternate explanation for symptoms prior to final adjudication.*
- *Neurologic toxicity consisted of different neurologic and/or psychiatric manifestations with or without overlapping time courses. Duration of NT was calculated from time of onset of the first event until resolution of the last event.*

Treatment of NT

Management guidelines for NT recommended treatment with corticosteroids. Tocilizumab was not recommended for the treatment of neurotoxicity related to CAR T cell therapy unless CRS or MAS/HLH was also present.

Table 54 shows concomitant medication use for treatment of neurological toxicity in the lisocabtagene maraleucel-treated Analysis Set.

Table 54: Concomitant Medication Use for Treatment of Investigator- Identified Neurological Toxicity in Recipients of Lisocabtagene Maraleucel (N = 61).

Concomitant Medication	n (%)
• Tocilizumab and/or Corticosteroid	7 (12)
• Corticosteroids only (Dexamethasone)	7 (12)
• Tocilizumab only	0
• Tocilizumab and Corticosteroids	0

(Source: FDA analysis of ADCM dataset)

Myelodysplastic syndrome (MDS)

Subject (b) (6) was diagnosed with Grade 4 Myelodysplastic syndrome (MDS) on Study Day 386. Testing for JCAR017 transgene was performed on a bone marrow

biopsy. However, the presence or absence of JCAR017 transgene could not be adequately evaluated due to the poor quality of the bone marrow sample. Hence, insertion site analysis on DNA from the neoplastic tissue could not be performed.

Persistence of transgene in the peripheral blood was tested by qPCR to monitor for the potential risk of clonal outgrowth related to vector insertion. After Cmax on Day 15, transgene levels decreased from 12,138 copies/µg to 28 copies/ug on Day 365 and was below the limit of detection at the end of study visit on Day 729.

The final pathology conclusions from the bone marrow biopsy and aspirate that was performed at the time of the MDS diagnosis was compatible with a diagnosis of MDS.

Subject (b) (6) is patient who was diagnosed with DLBCL two years prior to entry in Study 017006 and received first-line treatment with R-CHOP with a best response of PR, which progressed. This subject was treated with lisocabtagene maraleucel at the age of 79 and achieved a best response of PR on Day 29 and progressed on Day 180. The subject received subsequent anti-cancer therapy with pembrolizumab with lack of response and radiation therapy.

Myelodysplastic syndrome (MDS) was diagnosed on Study Day 386. The event of MDS was reported as ongoing at the time of the end of the study visit. The subject entered the Long-Term Follow-Up study (GC-LTFU-001) and was still alive as of data cutoff date for the 90 Day Safety Update.

Reviewer comment(s)

The clinical review team could not conclude that MDS was caused by lisocabtagene maraleucel. This assessment was based on the following multifactorial considerations:

1) *Transgene testing on bone marrow biopsies was not conducted on this subject, because of the poor quality of the sample, hence insertion site analysis was also not conducted on the bone marrow as it is only conducted when the transgene is detected to identify the location and frequency of vector integration sites.*
2) *Persistence of transgene in the peripheral blood was tested by qPCR to monitor for the potential risk of clonal outgrowth related to vector insertion. After Cmax on Day 15, transgene levels decreased from 12,138 copies/µg to 28 copies/ug on Day 365 and was below the limit of detection at the end of study visit on Day 729.*
3) *The subject received alkylating agents (R-CHOP) and radiation therapy as part of the first-line therapy 2 years before lisocabtagene maraleucel and received subsequent anti-cancer therapy with pembrolizumab and radiation therapy 6 months after lisocabtagene maraleucel due to disease progression. Hence, the patient had a higher risk of developing MDS compared to the general population.*
4) *The subject was 79 years old at the time of lisocabtagene maraleucel infusion. MDS was diagnosed more than year after lisocabtagene maraleucel infusion when the subject was 80 years old, which also puts the subject at higher risk of MDS.*
5) *Additionally, one subject treated on Study BCM-003 on the standard therapy (HSCT) arm and did not receive lisocabtagene maraleucel developed MDS, probably due to the previous chemotherapy.*

Hence, the clinical review team could not conclude that MDS was caused by lisocabtagene maraleucel.

6.2.12.6 Clinical Test Results

- Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for replication competent retrovirus (RCR) and antibodies to lisocabtagene maraleucel.
- Toxicity grading was based on CTCAE version 4.03 criteria.

Table 55 shows treatment emergent hematology laboratory toxicity and Table 56 shows treatment emergent chemistry laboratory toxicity. The baseline laboratory assessment is defined as the last value taken prior to the first dose of conditioning chemotherapy.

Table 55: New or Worsening Hematologic Laboratory Abnormalities by Laboratory Shift Analysis in Study 017006.

2L LBCL Study 017006	Evaluable Subjects with Baseline Result	Maximum Post-baseline Treatment-emergent Laboratory Abnormality			
		All grade	Grade 3-4	Grade 3	Grade 4
Parameter	**n**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Lymphocyte count decreased	61	60 (98)	59 (97)	1 (2)	58 (95)
White blood cell decreased	61	58 (95)	50 (82)	21 (34)	29 (48)
Neutrophil count decreased	61	56 (92)	49 (80)	14 (23)	35 (57)
Anemia	61	53 (87)	18 (30)	18 (30)	0
Platelet count decreased	61	44 (72)	16 (26)	4 (6)	12 (20)
Lymphocyte count increased	61	1 (2)	0	0	0

(Source: Adapted from response to FDA IR dated 26APR2022, Table 20.T.5.2.1.1)

Grade 4 laboratory abnormalities in ≥ 10% of patients were lymphocyte decrease (95%), neutrophil decrease (57%), and platelet decrease (20%).

Table 56: New or Worsening Chemistry Laboratory Abnormalities by Laboratory Shift Analysis in Study 017006.

2L LBCL Study 017006	Evaluable Subjects with Baseline Result	Maximum Post-baseline Treatment-Emergent Laboratory Abnormality			
		All grade	Grade 3-4	Grade 3	Grade 4
Parameter	n	n (%)	n (%)	n (%)	n (%)
Hypoalbuminemia	61	25 (41)	0	0	0
Hyponatremia	61	24 (39)	3 (5)	3 (5)	0
Hypomagnesemia	61	22 (36)	0	0	0
Aspartate aminotransferase increased	61	21 (34)	1 (2)	1 (2)	0
Hypophosphatemia	61	18 (30)	4 (7)	4 (7)	0
Alanine aminotransferase increased	61	17 (28)	0	0	0
Hypokalemia	61	16 (26)	1 (2)	1 (2)	0
Creatinine increased	61	8 (13)	0	0	0
Blood bilirubin increased	61	4 (7)	1 (2)	1 (2)	0
Hyperkalemia	61	3 (5)	1 (2)	0	1 (2)
Hypernatremia	61	3 (5)	0	0	0

2L LBCL Study 017006	Evaluable Subjects with Baseline Result	Maximum Post-baseline Treatment-Emergent Laboratory Abnormality			
		All grade	Grade 3-4	Grade 3	Grade 4
Parameter	n	n (%)	n (%)	n (%)	n (%)
Hypermagnesemia	61	2 (3)	0	0	0
Hyperuricemia	61	2 (3)	2 (3)	2 (3)	0

(*Source: Adapted from response to FDA IR dated 26APR2022 Table 20.T.5.2.2.1)*

Reviewer comment(s)

The key hematologic and chemical laboratories abnormalities were comparable across the other lisocabtagene maraleucel studies (BCM-003 and 017001). No additional safety concerns were noted from second-line therapy for LBCL in the transplant-ineligible population.

6.2.12.7 Dropouts and/or Discontinuations

Please see section 6.2.11.4, Table 45

- **6.2.13 Study Summary and Conclusions**

Study 017006

The efficacy of lisocabtagene maraleucel was evaluated in a single-arm, open-label, multicenter trial (PILOT; NCT03483103) in patients with refractory or relapsed LBCL after failure of first-line chemoimmunotherapy. The study enrolled patients who were transplant non-eligible due to age or comorbidities, while also having adequate organ function for CAR-T cell therapy. The study required at least one of the following criteria: age ≥ 70 years, adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; LVEF < 50%; creatinine clearance < 60mL/min; AST or ALT greater than 2 × ULN, or ECOG PS of 2. The planned dose of lisocabtagene maraleucel was 100 × 10^6 CAR-positive viable T cell (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells).

Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. 32/61 (53%) subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set received bridging therapy for disease control prior to lymphodepletion while lisocabtagene maraleucel was being manufactured. One subject (2%) had a CR after receiving bridging therapy. This subject went on to receive lisocabtagene maraleucel after disease relapse.

Lisocabtagene maraleucel was administered two to seven days following completion of lymphodepleting chemotherapy (LDC). The LDC regimen consisted of fludarabine 30 mg/m2/day and cyclophosphamide 300 mg/m2/day concurrently for 3 days. Lisocabtagene maraleucel was administered in the inpatient (67%) and outpatient (33%) setting.

Of 74 patients who underwent leukapheresis, 61 (82%) received lisocabtagene maraleucel and comprise the main efficacy population; 1 (1.4%) received lisocabtagene maraleucel that did not meet the product specifications for lisocabtagene maraleucel (manufacturing failure); and 12 (16%) did not receive lisocabtagene maraleucel for other reasons, mainly death from progressive disease or adverse events from bridging chemotherapy.

Of the 61 patients who received lisocabtagene maraleucel, the median age was 74 years

(range: 53 to 84 years), male (61%), white (89%), Asian (3%), and black (2%). Diagnoses included de novo DLBCL NOS (51%), high-grade B-cell lymphoma (33%), and DLBCL arising from follicular lymphoma (15%). Of these patients, 52% had primary refractory disease, 23% had relapse within 12 months of completing first-line therapy, and 25% had relapse >12 months after first-line therapy.

Efficacy:

The primary efficacy endpoint in Study 017006 was overall response rate (ORR) as assessed by the Independent Review Committee (IRC), defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial response (PR) based on Lugano 2014 criteria. The BOR was defined as the best disease response recorded from the time of lisocabtagene maraleucel infusion until disease progression, end of study, the start of another anticancer therapy. Best response was assigned according to the following order: CR, PR, stable disease (SD), progressive disease (PD), not evaluable, or not done.

The key secondary efficacy endpoints included the CR rate (proportion of subjects with BOR of CR), duration of response (DOR), DOR if BOR is CR.

All efficacy analyses were conducted on the lisocabtagene maraleucel-treated Efficacy Analysis Set (n=61), which included all subjects who received at least one infusion of lisocabtagene maraleucel investigational product and had PET-positive disease present before lisocabtagene maraleucel infusion per IRC assessment.

The ORR was 49/61 (80%) (95% CI: 68% to 89%) according to Lugano criteria based on IRC assessment with a CR rate of 33/61 (54%) (95% CI: 41 to 67). The median time to first response was one month (range 0.8 to 3.0 months). The median DOR was 11.20 months (95% CI: 5.06 to not reached [NR]). After the initial response, the probability of continued response at 6 months and 12 months was 62% (95% CI: 46 to 74) and 49% (95% CI: 31 to 64), respectively. The median duration of follow-up for DOR was 11.2 months (95% CI: 8.1 to 15.5)

Among the 33 subjects achieving CR as best overall response (BOR), the median DOR was NR (95% CI: 11.20 to NR), whereas in the 16 subjects achieving PR as their BOR, the median DOR was 2.1 months (95% CI: 1.4 to 2.3).

In the subjects who achieved a CR, the probability of continued response was 83% (95% CI: 64 to 93) at 6 months, 68% (95% CI: 45 to 83) at 12 months, and 60% (95% CI: 34 to 78) at 18 months.

Safety:

All summaries of safety data were conducted using lisocabtagene maraleucel-treated Efficacy Analysis Set. AEs were analyzed with a focus on treatment-emergent adverse events (TEAEs), defined as any AE that started on the day of lisocabtagene maraleucel infusion through (and including) 90 days after. Any AE that occurred after the initiation of another anticancer treatment or lisocabtagene maraleucel retreatment was not considered to be a TEAE.

Safety analysis: The safety population for the lisocabtagene maraleucel included 61 subjects that received conformal product and were treated with one dose.

In summary:

- The most common non-laboratory adverse reactions (incidence ≥ 20%) included

fatigue, cytokine release syndrome (CRS), nausea, hypotension, dyspnea.
- The most comment Grade 3 or 4 laboratory hematologic abnormalities (incidence ≥10%) included: lymphopenia (97%), leukopenia (82%), neutropenia (80%), anemia (30%), and thrombocytopenia (26%).
- The most comment Grade 3 or 4 laboratory chemistry abnormalities (incidence ≥10%) included: hypoalbuminemia (41%), hyponatremia (39%), hypermagnesemia (36%), AST increased (34%), hypophosphatemia (30%), ALT increased (28%), hypokalemia (26%), Creatinine increased (13%).
- Grade 3 or higher adverse reactions occurred in 48 (79%) subjects.
- Three subjects had fatal adverse events after lisocabtagene maraleucel: two subjects died of COVID 19 at the peak of the pandemic and one subject died of sepsis.
- Most common Grade 3 or higher AESI included: prolonged cytopenias 19 (31%), neurologic toxicities 4 (7%), and CRS 1 (2%).
- Any grade CRS occurred in 25 (41%) subjects, and any grade neurologic toxicity occurred in 19 (31%) subjects.

No new safety signals were identified in this submission. CRS and neurologic toxicity associated with lisocabtagene maraleucel are serious, life-threatening and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks.

Due to the lack of long-term safety data in the sBLA, a postmarketing long-term follow-up registry study to fulfil the 017001 post-marketing requirement will enroll 1500 DLBCL patients. Follow up of patients for 15 years in this study will provide long-term safety data.

To enhance the safety of lisocabtagene maraleucel, the following measures were followed:

- The product label includes a boxed warning for CRS and NT, and the warnings and precautions section conveys the treatment algorithm for CRS and NT management.
- Daily monitoring following lisocabtagene maraleucel infusion for 7 days was included in the label.
- REMS with ETASU were included in the label to assure the safe use of lisocabtagene maraleucel.

In summary, 017006 represents an adequate and well-controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval.

The review team recommends granting regular approval for lisocabtagene maraleucel for the treatment of adult patients with primary refractory or relapsed LBCL after first-line chemoimmunotherapy and who are non-eligible for HSCT due to age or comorbidities.

7. INTEGRATED OVERVIEW OF EFFICACY

Although the differences in the study designs, patient populations, and endpoints in the BCM-003 study and Study 017006 do not permit a robust pooled efficacy assessment, the treatment effect in terms of response rate and CR rate, as well as the finding that durable remissions tend to be restricted to patients who achieve CR, are consistent between these studies, as well as across all three studies of lisocabtagene maraleucel evaluated. The following sections provide an indication-specific assessment of efficacy in the studies supporting a second-line indication for lisocabtagene maraleucel, followed by an assessment of efficacy across all three trials that have supported indications in R/R LBCL. Given the absence of efficacy and safety data in primary CNS lymphoma, the LOU for the originally approved indication is maintained for the second-line indications. The totality of data from the second-line and later-line settings supports regular approval of lisocabtagene maraleucel for the following indications:

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; 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; or
- relapsed or refractory disease after two or more lines of systemic therapy.

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

7.1 Recommended Second-Line Indications

- **Adult patients with LBCL who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.**

Clinical benefit was established in BCM-003, a Phase 3, randomized, open label, multicenter study of second-line therapy of LBCL, that randomized 184 subjects in a 1:1 ratio to either a single infusion of lisocabtagene maraleucel (preceded by lymphodepleting chemotherapy) or to standard therapy. All subjects had either primary refractory disease or relapse within 12 months of completing first-line therapy, were potentially eligible for autologous HSCT, and had not yet received second-line treatment. Standard therapy consisted of protocol defined, platinum-based chemoimmunotherapy for three cycles followed by high-dose chemotherapy and autologous HSCT in subjects achieving CR or PR.

The primary endpoint was EFS determined by a blinded IRC. Key secondary endpoints were CRR, PFS per IRC and OS. Altogether, 74% of the study population had primary refractory disease, 27% had early relapsed disease; the most common NHL types were de novo DLBCL (64%), high-grade B-cell lymphoma (23%) and primary mediastinal B-cell lymphoma (10%).

A total of 92 subjects were randomized to the lisocabtagene maraleucel arm and 89

subjects (97%) received conforming product. ORR per central assessment in lisocabtagene maraleucel treated subjects was 86% (79/92) with CR rate of 66% (61/92). Ninety-two subjects were randomized to the standard therapy arm out of which 91 subjects (99%) received any protocol specified chemoimmunotherapy; 48% (out of 92) of the subjects that received any protocol specified therapy responded per central assessment with a CR rate of 39%. 47% (42 out of 92) of the treated subjects underwent HSCT. The reasons for not proceeding with HSCT include lack of efficacy, disease progression, physician decision, death, AE.

There is a clear difference in the proportion of subjects receiving definitive treatment between the two arms, 97% of subjects randomized to lisocabtagene maraleucel arm received the CAR-T therapy versus 47 % subjects in the standard therapy arm underwent HSCT. There are two reasons that might explain the difference in receiving the definitive therapy 1) single CAR-T dose infusion versus multiple cycles of chemotherapy and 2) the refractoriness of the enrolled population.

EFS was significantly improved for lisocabtagene maraleucel arm compared to the standard therapy arm with a stratified HR of 0.34 (95% CI:0.22, 0.51) and a p- value <0.0001. The median EFS in the lisocabtagene maraleucel arm was 10.1 months (95% CI: 6.1, NR) compared to 2.3 months (95% CI: 2.2, 4.3) in the standard therapy arm. The estimated 24-month EFS was 38% (95% CI: 21.3, 54.8) vs. 18% (95% CI: 7.4, 31.9) in the standard therapy arm respectively.

The most common EFS event in both the lisocabtagene maraleucel arm and standard therapy arm was disease progression (28% and 42%). Failure to achieve CR or PR by 9 weeks post-randomization was the second most common EFS in the standard therapy arm 19% vs 4% in lisocabtagene maraleucel arm.

The IRC-assessed complete response (CR) rate was statistically significantly higher at 66% (95% CI: 56, 76) in the lisocabtagene maraleucel arm compared to 39% (95% CI: 29, 50) in the standard therapy arm (p-value < 0.0001). The PFS also favored the lisocabtagene maraleucel arm (14.8 months; 95% CI: 6.6, NR) compared to the standard therapy arm (5.7 months; 95% CI: 3.9, 9.4). The interim OS analysis performed at 82% information level, was not statistically significant. OS tended to favor lisocabtagene maraleucel with a HR of 0.509 (95% CI: 0.258, 1.004), one-sided p-value = 0.0257. Updates to OS are planned for the primary analysis

Study BCM-003 design was limited to assess superiority of lisocabtagene maraleucel compared to HSCT in subjects with chemo sensitive relapse who were candidates to undergo HSCT. Subjects were randomized in advance to the two treatments arms, bridging therapy with any of the standard therapy platin based chemotherapy was allowed in the lisocabtagene maraleucel arm. Almost half of the patients in the standard therapy arm responded to the chemotherapy and underwent HSCT. In ZUMA-7, the exploratory analysis performed in the 62 subjects in the standard therapy arm with chemo sensitive disease that underwent HSCT indicates a median EFS of 12 months (95% CI: 8.5, NE) and 1-year EFS of 52% (95% CI: 38, 64) which is at least comparable to the historical data for HSCT in the second-line setting.

In conclusion, BCM-003 is an adequate and well-controlled study that provides substantial evidence of efficacy of lisocabtagene maraleucel compared to standard therapy in patients with primary refractory and early relapsed LBCL based on consistent improvement in EFS, PFS, ORR, and CR rate and supported by OS.

The magnitude of clinical benefit observed with lisocabtagene maraleucel is the basis for recommended regular approval. Because the study enrolled patients with primary refractory and early relapsed LBCL (within 1 year of first-line chemoimmunotherapy), the recommended indication is restricted to adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first- line chemoimmunotherapy.

- **Adult patients with LBCL who have 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.**

The efficacy of lisocabtagene maraleucel was evaluated in a single-arm, open-label, multicenter trial (PILOT; NCT03483103) in patients with refractory or relapsed LBCL after failure of first-line chemoimmunotherapy. The study enrolled patients who were transplant non-eligible due to age or comorbidities, while also having adequate organ function for CAR-T cell therapy. The study required at least one of the following criteria: age ≥ 70 years, adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; LVEF < 50%; creatinine clearance < 60mL/min; AST or ALT greater than 2 × ULN, or ECOG PS of 2. The planned dose of lisocabtagene maraleucel was 100 × 10^6 CAR-positive viable T cell (50 × 10^6 CD8+ CAR+ T cells and 50 × 10^6 CD4+ CAR+ T cells).

Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy. 32/61 (53%) subjects in the lisocabtagene maraleucel-treated Efficacy Analysis Set received bridging therapy for disease control prior to lymphodepletion while lisocabtagene maraleucel was being manufactured. One subject (2%) had a CR after receiving bridging therapy. This subject went on to receive lisocabtagene maraleucel after disease relapse.

Lisocabtagene maraleucel was administered two to seven days following completion of lymphodepleting chemotherapy (LDC). The LDC regimen consisted of fludarabine 30 mg/m2/day and cyclophosphamide 300 mg/m2/day concurrently for 3 days. Lisocabtagene maraleucel was administered in the inpatient (67%) and outpatient (33%) setting.

Of 74 patients who underwent leukapheresis, 61 (82%) received lisocabtagene maraleucel and comprise the main efficacy population; 1 (1.4%) received lisocabtagene maraleucel that did not meet the product specifications for lisocabtagene maraleucel (manufacturing failure); and 12 (16%) did not receive lisocabtagene maraleucel for other reasons, mainly death from progressive disease or adverse events from bridging chemotherapy.

Of the 61 patients who received lisocabtagene maraleucel, the median age was 74 years (range: 53 to 84 years), male (61%), white (89%), Asian (3%), and black (2%). Diagnoses included de novo DLBCL NOS (51%), high-grade B-cell lymphoma (33%), and DLBCL arising from follicular lymphoma (15%). Of these patients, 52% had primary refractory disease, 23% had relapse within 12 months of completing first-line therapy, and 25% had relapse >12 months after first-line therapy.

The primary efficacy endpoint in Study 017006 was overall response rate (ORR) as assessed by the Independent Review Committee (IRC), defined as the proportion of subjects with a best overall response (BOR) of either complete response (CR) or partial

response (PR) based on Lugano 2014 criteria. The BOR was defined as the best disease response recorded from the time of lisocabtagene maraleucel infusion until disease progression, end of study, the start of another anticancer therapy. Best response was assigned according to the following order: CR, PR, stable disease (SD), progressive disease (PD), not evaluable, or not done.

The secondary efficacy endpoints included CR rate, duration of response (DOR), and DOR if BOR is CR.

All efficacy analyses were conducted on the lisocabtagene maraleucel-treated Efficacy Analysis Set (n=61), which included all subjects who received at least one infusion of lisocabtagene maraleucel investigational product and had PET-positive disease present before lisocabtagene maraleucel infusion per IRC assessment.

The ORR was 49/61 (80%) (95% CI: 68% to 89%) according to Lugano criteria based on IRC assessment with a CR rate of 33/61 (54%) (95% CI: 41 to 67). The median time to first response was one months (range 0.8 to 3.0 months). The median DOR was 11.20 months (95% CI: 5.06 to not reached [NR]). After the initial response, the probability of continued response at 6 months and 12 months was 62% (95% CI: 46 to 74) and 49% (95% CI: 31 to 64), respectively. The median duration of follow-up for DOR was 11.2 months (95% CI: 8.1 to 15.5)

Among the 33 subjects achieving CR as the BOR, the median DOR was NR (95% CI: 11.20 to NR), whereas in the 16 subjects achieving PR as their BOR, the median DOR was 2.1 months (95% CI: 1.4 to 2.3).

In the subjects who achieved a CR, the probability of continued response was 83% (95% CI: 64 to 93) at 6 months, 68% (95% CI: 45 to 83) at 12 months, and 60% (95% CI: 34 to 78) at 18 months.

In summary, study 017006 represents an adequate and well-controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval of BREYANZI for the treatment of adult patients with primary refractory or relapsed LBCL after first-line chemoimmunotherapy and who are ineligible for HSCT due to age or comorbidities.

7.2 Efficacy Across Trials

Table 57 shows the IRC-assessed ORR and durability of response after lisocabtagene maraleucel infusion in LBCL in three studies.

Table 57 Response Rate and Durability of Response with Lisocabtagene Maraleucel in 3 Studies.

Parameter	TRANSFORM	PILOT	TRANSCEND
n	92	61	192
Recommended Dose of CAR T cells	(90-110) x 10^6	(90-110) x 10^6	(50-110) x 10^6
Indication in subjects with LBCL	refractory to 1L chemoimmunotherapy or relapse within 12 months of achieving CR to first-line chemoimmunotherapy	refractory to 1L chemoimmunotherapy or relapse after 1L chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age	relapsed or refractory disease after two or more lines of systemic therapy
Duration of Follow up (FU)			
Median Duration of FU (months)	4.3	11.2	16.4
95% CI	(3.6-6.9)	(8, 16)	(11.7, 17.7)
ORR (CR+PR)			
ORR	79/92 (86)	49/61 (81)	141/192 (73)
95% CI	(77,92)	(68, 90)	(67,80)
Median DOR (months)	12.6	11.20	16.7
95% CI	(5.7, NR)	(5.06, NR)	(6.0, NR)
CR			
CR rate n (%)	61/92 (66)	33/61 (54)	104/286 (54)
95% CI	(56,76)	(41, 67)	(47,61)
Median DOR (months)	NR	NR	NR
95% CI	(7.85, NR)	(11.20, NR)	(16.7, NR)
PR			
PR rate n (%)	18/92 (20)	16/61 (26)	37/192 (19)
95% CI	(12, 29)	(16, 39)	(14,26)
Median DOR (months)	2.33	2.10	1.4
95% CI	(2.07, NR)	(1.38-2.30)	(1.1, 2.2)

(Source: FDA analysis)

Even though the efficacy data as assessed by IRC could not be pooled between the three studies (2L trials: TRANSFORM and PILOT) and (3L and higher trial: TRANSCEND) due to the difference in the study design and primary endpoints, we observed consistency of responses and durability of responses among the 3 studies. Of particular interest, the three studies consistently showed:

- High overall response rate (73%-86%)
- High CR rate (54%-66%).
- Clinically meaningful DOR (median 11.2 -16.7 months)
- Brief median DOR if the BOR is PR (1.4- 2.3 months) in contrast to the significant DOR if the BOR is CR (median NR).

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Applicant submitted additional supportive safety data for studies of lisocabtagene maraleucel in subjects with large B-cell lymphoma (Study 017001). We analyzed the data from the 3 studies (BCM-003, 017006, and 017001) but no new safety signal was identified. Study 017001 was the primary study for the approved LBCL indication, and the data were reviewed in the original BLA submission. The ISS dataset was used to generate the adverse events of special interest that will be reflected in the label.

8.2 Safety Database

- **8.2.1 Studies/Clinical Trials Used to Evaluate Safety**

Table 58 lists the 3 clinical trials that included in the safety population of lisocabtagene maraleucel (N=418).

Table 58: Clinical Trials to Evaluate Safety of Lisocabtagene Maraleucel (N=418)

Study No.	Primary Objective	Study Design	Dosage	No. of Subjects	Subject Population	Study Status
Study 017001	Safety	Single-arm, open-label, multicenter Phase 1 study	Dose Cohorts: DL1S: 50 x10^6 DL2S:100x10^6	268	R/R DLBCL after failure of two or more prior lines of systemic therapy	Completed
Study BCM –003	Safety Efficacy	Phase 3, randomized, open-label, parallel-group, multicenter trial	Single dose JCAR017 (100×10^6 CAR+ T cells) IV	89	R/R aggressive NHL after failure of 1 line of prior therapy	Ongoing Primary CSR, (data cutoff 08 Mar 2021)
Study 017006	Safety Efficacy in HSCT ineligible	Phase 2, open label, single-arm multicenter trial	Single dose JCAR017 (100×10^6 CAR+ T Cells) IV	61	R/R aggressive NHL after failure of 1 line of prior therapy in transplant ineligible adults	Ongoing Interim CSR (data cutoff 28 May 2021)

Source: sBLA 125714/90 Module 5.2: Tabular listing of Clinical Studies; modified Table 1

- **8.2.2 Overall Exposure, Demographics of Pooled Safety Populations**

Baseline demographics and disease characteristics of the pooled safety population (n=418) are displayed in Table 59.

Table 59: Baseline Demographics and Disease Characteristics of the Pooled Safety Population (N=418).

Parameter	2L and 3L + LBCL N=418
Age (years) [a]	
n	418
Mean (StD)	62 (13)
Median (Min, Max)	64 (18, 86)
Age Group, n (%)	
< 65 years	218 (52)
≥ 65 to < 70 years	65 (16)
≥ 70 to < 75 years	80 (19)
≥ 75 years	55 (13)
Screening ECOG PS, n (%)	
0	176 (42)
1	222 (53)
2	20 (5)
Sex, n (%)	
Female	165 (39)
Male	253 (61)
Race, n (%)	
White	337 (81)
Unknown	36 (9)
Asian	23 (6)
Black or African	17 (4)
Refractory/ relapsed disease n (%)	
Refractory [a]	311 (74)
Relapsed	107 (26)
Active CNS disease status n (%)	
Yes	8 (2)
No	407 (97)
Unknown	3 (1)

[a] refractory disease: if a subject achieved PD, SD, PR, or CR lasting < 3 months following 1L therapy; otherwise the status was relapsed
(Source: FDA analysis of ADSL.xpt from ISS)

- **8.2.3 Categorization of Adverse Events**

The same FDA grouped terms were used to recode the adverse events that were coded in dictionary code adverse events columns in adverse event data sets. A copy of the FDA grouped terms was sent to the Applicant to add a column to the datasets with the FDA grouped terms. The pooled analysis of the safety data that was summarized from the three studies was based on the agreed upon FDA grouped terms.

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

There are inherent limitations with any pooling of data across studies due to potential differences in patient, disease, and treatment characteristics, differences in sample size and thus the precision of the estimates, and other factors. These limitations extend to pooling of rates of AESIs, as done in the Warnings and Precautions section of the USPI to inform CRS rates, neurotoxicity rates, infection rates, and other outcomes. For example, the dose of CAR-T cells, which correlates with the rate and severity of CRS and

neurotoxicity, was generally lower in the first registrational trial (Study 17001) than the trials in the second-line setting. Additionally, over time there has been increased recognition of CRS and NT, coupled with a shift toward earlier implementation of tocilizumab for treatment of Grade 1 or 2 CRS, that limits comparisons of safety in the second-line vs. later-line setting. Nevertheless, when rates of AESIs are comparable across studies, pooling is helpful for characterizing the general tolerability of the regimen.

8.4 Safety Results

- **8.4.1 Deaths**

Table 60 shows the incidence of deaths reported in the safety population (N=418 subjects) in the 3 lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 60: Summary of Deaths After 2L and Later Treatment with Lisocabtagene Maraleucel

Parameter	BCM-003 N = 89	17006 N = 61	17001 N = 268	Total N=418
All Deaths	13 (15%)	18 (30%)	114 (42%)	140 (33%)
Disease Progression	7 (8%)	15 (25%)	96 (36%)	117 (28%)
Adverse Events	2 (2%)	3 (5%)	12 (4%)	17 (4%)
Other Causes	3 (3%)	0	3 (1%)	7 (2%)
Unknown	1 (1)	0	3 (1%)	4 (1%)
Fatal AEs ≤ 30 days after CAR-T infusion	0	0	5 (1%)	5 (1%)
Fatal AEs > 30 days after CAR-T infusion	4*(4%)	3*(5%)	7 (3%)	14 (3%)

Abbreviations: AE = adverse event; 2L= second line; 3L = third line
Source: FDA analysis of ADSL, ADDD and clinical review memo for original BLA 125714.0
**Including COVID deaths*

Amongst the 418 subjects treated with lisocabtagene maraleucel, five subjects or 1% died within 30 days of CAR-T cell infusion. Disease progression was the most common cause of deaths (33%) in the safety population as expected during treatment of refractory or relapsed LBCL.

- **8.4.2 Nonfatal Serious Adverse Events**

Table 61 shows the pooled, nonfatal, serious adverse events in 418 subjects who received lisocabtagene maraleucel in the three studies.

Table 61: Nonfatal Serious Adverse Events in Recipients of Lisocabtagene Maraleucel Across Studies

System Organ Class and Preferred Term	BCM-003 N=89 n (%)	17006 N=61 n (%)	17001 N=268 n (%)	Total N= 418 n (%)
Subjects with any serious TEAE	34 (38)	20 (33)	122 (46)	176 (42)
Blood and lymphatic system disorders	14 (16)	1 (2)	25 (9)	35 (8)
Febrile neutropenia	14 (16)	1 (2)	25 (9)	40 (10)
Immune system disorders	12 (14)	8 (13)	49 (18)	69 (17)
Cytokine release syndrome	12 (14)	8 (13)	49 (18)	69 (17)
Nervous system disorders	5 (6)	1 (2)	41 (15)	47 (11)
Encephalopathy	2 (2)	1 (2)	12 (5)	15 (4)
Aphasia	2 (2)	0	9 (3)	11 (3)
Tremor	1 (1)	0	3 (1)	4 (1)
Infections and infestations	14 (16)	5 (8)	28 (10)	47 (11)
Infections with pathogen unspecified	7 (8)	3 (5)	24 (9)	34 (8)
Bacterial infectious disorders	5 (6)	2 (3)	14 (5)	22 (5)
Viral infectious disorders	3 (3)	0	4 (2)	7 (2)
Fungal infectious disorders	0 (0)	0 (0)	3 (1)	3 (1)
Psychiatric disorders	0	3 (5)	20 (8)	23 (6)

System Organ Class and Preferred Term	BCM-003 N=89 n (%)	17006 N=61 n (%)	17001 N=268 n (%)	Total N= 418 n (%)
Confusional state	0	3 (5)	8 (3)	11 (3)
Mental status changes	0	0	7 (3)	7 (2)
Respiratory, thoracic and mediastinal disorders	2 (2)	2 (3)	12 (5)	16 (4)
Pulmonary embolism	2 (2)	2 (3)	1 (0.4)	5 (1)
Dyspnea	0	0	15 (6)	15 (4)

(Source: adapted from SCS, Table 6.1.3.5-1)

Reviewer comment(s)

The incidence of nonfatal serious adverse events was comparable among the three studies.

- **8.4.3 Study Dropouts/Discontinuations**

Table 62 shows the disposition of the safety population (N=418 subjects) in the 3 lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 62: Subject Disposition of the Combined Safety Population (N=418).

Study Status	BCM-003 N=89 n (%)	017006 N=61 n (%)	017001 N=268 n (%)	Total N=418 n (%)
Ongoing	77 (87)	32 (52)	122 (46)	231 (55)
Completed study	0	5 (8)	24 (9)	29 (7)
Enrolled in the long-term follow-up study	1	2 (3.3)	15 (6)	19 (5)
Discontinued from study	12 (14)	24 (39)	122 (46)	158 (38)
Death	10 (11)	18 (29)	114 (43)	142 (34)
Adverse event	0	0	0	0
Lost to follow-up	0	0	2 (0.7)	2 (0.5)
Other	1 (1)	1 (2)	0	2 (0.5)
Subject withdrew consent	1 (1)	5 (8)	6 (2)	12 (3)

Source: Modified from ISS Table 6.1.2.1-1

No subjects had interruption or discontinuation of lisocabtagene maraleucel due to infusional or other toxicities.

- **8.4.4 Common Adverse Events**

Table 63 shows the incidence of TEAEs (Grade 1- 5) that occurred in ≥ 10% of the safety population (N=418 subjects) in the 3 lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 63: Integrated Summary of Any-Grade AEs in >10% of 418 Subjects Treated with Lisocabtagene Maraleucel.

AE grouped term defined by FDA	All AEs (Grade 1 – 5) n (%)
Nausea	294 (70)
Fatigue	289 (69)
Cytokine release syndrome	250 (60)
Musculoskeletal pain	227 (54)
Constipation	195 (47)
Headache	193 (46)

AE grouped term defined by FDA	All AEs (Grade 1 – 5) n (%)
Edema	175 (42)
Diarrhea	159 (38)
Encephalopathy	159 (38)
Abdominal pain	148 (35)
Fever	148 (35)
Decreased appetite	145 (35)
Vomiting	138 (33)
Hypotension	132 (32)
Pain	129 (31)
Dizziness	127 (30)
Cough	120 (29)
Dyspnea	117 (28)
Tachycardia	107 (26)
Insomnia	99 (24)
Upper respiratory tract infection	87 (21)
Infections - pathogen unspecified	82 (20)
Rash	82 (20)
Tremor	80 (19)
Neuropathy peripheral	75 (18)
Hypogammaglobulinemia	62 (15)
Chills	57 (14)
Renal failure	57 (14)
Bacterial infection	56 (13)
Motor dysfunction	55 (13)
Delirium	52 (12)
Aphasia	51 (12)
Cardiac Arrhythmias	45 (11)
Fungal infection	45 (11)
Hemorrhage	44 (11)

(Source: FDA analysis of ISS ADAE dataset)

Other clinically important Grade 1-5 AEs that occurred in <10% of the subjects treated with lisocabtagene maraleucel in the 3 clinical trials include: Thrombosis (9%), Ataxia (8%), Pneumonia (7%), Urinary tract infection (7%), Vision blurred (6%), Gastrointestinal hemorrhage (5%), Hemophagocytic lymphohistiocytosis (3%), Paresis (2%), Herpes viral infections (2%), Pericardial effusion (2%), Cardiac failure (1%), Seizure (1%).

Reviewer comment(s)

Only relevant incidence included in the label are included in this table.

Table 64 shows the incidence of TEAEs (Grade 3 or higher) that occurred in ≥ 2% of the

safety population (N=418 subjects) in the 3 lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 64: Grade 3 and Higher AEs in ≥2% of 418 Subjects Treated with Lisocabtagene Maraleucel

PT or FDA grouped PT	Grade 3 and higher AEs n (%)
Infections - pathogen unspecified	65 (16)
Encephalopathy	45 (11)
Sepsis	27 (6)
Dyspnea	24 (6)
Hypertension	22 (5)
Pneumonia	21 (5)
Musculoskeletal pain	19 (5)
Hypotension	19 (5)
Bacterial infection	19 (5)
Fatigue	18 (4)
Cytokine release syndrome	16 (4)
Abdominal pain	16 (4)
Edema	15 (4)
Dizziness	15 (4)
Aphasia	14 (3)
Decreased appetite	13 (3)
Delirium	12 (3)
Urinary tract infection	11 (3)
Headache	10 (2)
Renal failure	10 (2)
Motor dysfunction	10 (2)
Cardiac Arrhythmias	9 (2)
Gastrointestinal hemorrhage	9 (2)
Nausea	8 (2)
Thrombosis	8 (2)
Hemophagocytic lymphohistiocytosis	7 (2)

(Source: FDA analysis of ISS ADAE dataset)

Other clinically important Grade 3 AEs that occurred in 1% of the subjects treated with lisocabtagene maraleucel in the three clinical trials are: tremors, peripheral neuropathy, viral infections, paresis, and seizures.

- **8.4.5 Clinical Test Results**

Table 65 shows the incidence of new or worsening laboratory abnormalities by lab shift treatment-emergent hematology laboratory results in the safety population (N=418 subjects) in the three lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 65: New or Worsening Hematologic Laboratory Abnormalities by Laboratory Shift Analysis

2L LBCL Study BCM-003 2L LBCL Study 017006 3L + LBCL 017001	Evaluable Subjects	Maximum Post-Baseline Grade			
		All grade	Grade 3-4	Grade 3	Grade 4
Parameter	**n**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
White blood cell decreased	417	409 (98)	375 (90)	139 (33)	236 (57)
Neutrophil count decreased	417	393 (94)	362 (87)	107 (26)	255 (61)
Lymphocyte count decreased	402	385 (96)	384 (96)	16 (4)	368 (92)
Platelet count decreased	417	312 (75)	168 (40)	69 (17)	99 (24)
Anemia	417	306 (73)	132 (32)	132 (32)	0
Lymphocyte count increased	402	10 (3)	0	0	0

(Source: Adopted from IR dated 04-26-2022. Table 20.T.5.2.1.1)

Table 66 shows the incidence of new or worsening chemistry abnormalities by lab shift analysis in the safety population (N=418 subjects) in the three lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 66: New or Worsening Chemistry Laboratory Abnormalities by Laboratory Shift Analysis

All studies: • 2L LBCL Study BCM-003 • 2L LBCL Study 017006 • 3L + LBCL 017001	Evaluable Subjects	Maximum Post-Baseline Grade			
		All grade	Grade 3-4	Grade 3	Grade 4
Parameter	n	n (%)	n (%)	n (%)	n (%)
Hypoalbuminemia	418	195 (47)	7 (2)	7 (2)	0
Hypophosphatemia	418	141 (34)	52 (12)	51 (12)	1 (0.2)
Hyponatremia	418	135 (32)	19 (5)	19 (5)	0
Hypomagnesemia	418	116 (28)	0	0	0
Aspartate aminotransferase increased	418	115 (28)	3 (1)	3 (1)	0
Alanine aminotransferase increased	418	110 (26)	5 (1)	5 (1)	0
Hypokalemia	418	110 (26)	11 (3)	10 (2)	1 (0.2)
Creatinine increased	418	48 (12)	1 (0.2)	1 (0.2)	0
Blood bilirubin increased	418	45 (11)	8 (2)	8 (2)	0
Hypermagnesemia	418	38 (9)	1 (0.2)	1 (0.2)	0
Hypernatremia	418	27 (7)	0	0	0
Hyperuricemia	417	17 (4)	14 (3)	12 (3)	2 (1)
Hyperkalemia	418	13 (3)	4 (1)	1 (0.2)	3 (1)

(Source: Adopted from IR dated 04-26-2022, Table 20.T.5.2.1.1)

Reviewer comment(s)

The key hematologic and chemical laboratories abnormalities are comparable across the three lisocabtagene maraleucel studies (BCM-003, 017006, and 01700). No additional safety concerns were noted from second-line therapy for LBCL. The clinical review team agrees to present the pooled data in the label.

- **8.4.6 Systemic Adverse Events**

Table 67 shows the incidence of AEs in the safety population (N=418 subjects) in the three lisocabtagene maraleucel studies (BCM-003, 017006 and 017001) combined.

Table 67: All Grade and Grade 3 and Higher Common AEs in 418 Recipients of Lisocabtagene Maraleucel

SOC / PT or FDA grouped PT	All Grade (Grade 1 – 5) AEs n (%)	Grade 3 and higher AEs n (%)
Blood and lymphatic disorders		
Febrile neutropenia	40 (11)	40 (11)
Cardiac disorders		
Tachycardia	106 (25)	1 (0)
Cardiac Arrhythmias	45 (11)	9 (2)
Pericardial effusion	7 (2)	1 (0)
Cardiac failure	6 (1)	3 (1)
Eye disorders		
Vision blurred	27 (6)	0 (0)
Gastrointestinal disorders		
Nausea	294 (70)	8 (2)
Constipation	195 (47)	1 (0)
Diarrhea	159 (38)	4 (1)
Abdominal pain	148 (35)	16 (4)
Gastrointestinal hemorrhage	20 (5)	9 (2)
General disorders and administration site conditions		
Fatigue	289 (69)	18 (4)
Fever	183 (44)	11 ()
Edema	144 (34)	7 (2)
Chills	57 (14)	0 (0)
Chest pain	21 (5)	1 (0)
Hemorrhage	3 (1)	1 (0)
Immune system disorders		
Cytokine release syndrome	191 (46)	22 (5)
Hypogammaglobulinemia	62 (15)	1 (0)
Hemophagocytic lymphohistiocytosis	9 (2)	4 (1)
Infections and infestations		
Infections – pathogen unspecified	82 (20)	34 (8)
Bacterial infections	56 (13)	22 (5)
Fungal infections	45 (11)	2 (0.5)
Viral infections	11 (3)	8 (2)
Metabolism and nutrition disorders		
Decreased appetite	145 (35)	13 (3)
Dehydration	41 (10)	5 (1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	227 (54)	19 (5)
Motor dysfunction	52 (12)	10 (2)
Nervous system disorders		
Headache	193 (46)	10 (2)

SOC / PT or FDA grouped PT	All Grade (Grade 1 – 5) AEs n (%)	Grade 3 and higher AEs n (%)
Dizziness	121 (29)	15 (4)
Encephalopathy	83 (20)	25 (6)
Tremor	80 (19)	4 (1)
Neuropathy peripheral	75 (18)	4 (1)
Aphasia	46 (11)	14 (3)
Ataxia	19 (5)	1 (0)
Paresis	9 (2)	4 (1)
Seizure	6 (1)	4 (1)
Psychiatric disorders		
Delirium	52 (12)	12 (3)
Renal and urinary disorders		
Renal failure	39 (9)	10 (2)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	117 (28)	24 (6)
Skin and subcutaneous tissue disorders		
Rash	75 (18)	3 (1)
Vascular disorders		
Hypotension	132 (32)	19 (5)
Thrombosis	28 (7)	3 (1)

(Source: FDA analysis of ISS ADAE dataset)

Reviewer comment(s)

The safety data and key AEs are comparable across the three lisocabtagene maraleucel studies (BCM-003, 017006, and 01700). No additional safety concerns were noted from second-line therapy for LBCL. The clinical review team agrees to present the pooled data in the label.

- **8.4.7 Local Reactogenicity**

No local reactions were reported after lisocabtagene maraleucel infusion.

- **8.4.8 Adverse Events of Special Interest**

Table 68 shows the adverse events of special interest (AESIs) by FDA grouped preferred terms in 418 subjects who received lisocabtagene maraleucel across studies (BCM-003, 017006 and 017001).

Table 68: AEs of Special Interest in 418 Recipients of Lisocabtagene Maraleucel.

TEAEs	N=418 Grade 1-5 % (N)	N=418 Grade ≥3 % (N)
Subjects with any CRS	191 (46)	15 (3.5%)
CRS symptoms		
fever	183/191 (96)	11/191 (6)
hypotension	83/191 (43)	11/191 (6)
tachycardia	55/191 (29)	1/191 (1)
chills	44/191 (23)	0
hypoxia	32 (17)	14 (7)

TEAEs	N=418 Grade 1-5 % (N)	Grade ≥3 % (N)
Headache	24 (13)	5 (3)
Fatigue	24 (13)	1 (1)
Subjects with any neurologic toxicity (NT)	136 (33)	42 (10)
NT symptoms		
Encephalopathy	83 (20)	25 (6)
Tremor	45 (11)	1 (0)
Aphasia	30 (7)	9 (2)
Headache	24 (6)	5 (1)
Dizziness	22 (5)	2 (0)
Delirium	21 (5)	5 (1)
Ataxia	17 (4)	1 (0)
Neuropathy peripheral	4 (1)	0 (0)
Motor dysfunction	3 (1)	1 (0)
Paresis	3 (1)	2 (0)
Seizure	3 (1)	3 (1)
Infections	170 (41)	54 (13)
Bacterial infections	56 (13)	22 (5)
Infections – pathogen unspecified	82 (20)	34 (8)
Febrile neutropenia	40 (10)	40 (10)
Fungal infections	45 (11)	2 (0.5)
Viral infections	11 (3)	8 (2)
Prolonged cytopenias	382 (91)	157 (3)
Neutropenia	373 (89)	94 (22)
Thrombocytopenia	172 (41)	127 (30)
Anemia	139 (33)	31 (7)
Hypogammaglobulinemia	62 (15)	1 (0)
Myelodysplastic syndrome	8 (2)	8 (2)

(Source: FDA analysis)

Time to onset and time to resolution of CRS

In patients (n=418) receiving lisocabtagene maraleucel in the three studies, the median time to CRS onset was 5 days (range: 1 to 63 days) (interquartile range [IQR]) of 3, 8). Median Time to resolution of CRS was 2 days (range: 1 to 16 days) (interquartile range [IQR]) of 1, 4).

Time to onset and time to resolution of NT

In patients (n=418) receiving lisocabtagene maraleucel in the three studies, the median time to onset of NT was 8 days (range: 1 to 63 days) (interquartile range [IQR]) of 8, 17). Median Time to resolution of NT was 11 days (range: 1 to 119 days). (Interquartile range [IQR]) of 3, 21).

Of patients developing neurotoxicity, 77% (105/136) also developed CRS.

Reviewer comment(s)

The AESIs are comparable across the three lisocabtagene maraleucel studies (BCM-003, 017006, and 01700). No additional safety concerns were noted from second-line therapy for LBCL. The clinical review team will present the pooled data in the label.

8.5 Additional Safety Evaluations

- **8.5.1 Dose Dependency for Adverse Events**

Not applicable. There was a single dose that was used to treat the subjects on Study BCM-003 and Study 017006.

- **8.5.2 Time Dependency for Adverse Events:** Not applicable.
- **8.5.3 Product-Demographic Interactions:** Not applicable.
- **8.5.4 Product-Disease Interactions:** Not applicable.
- **8.5.5 Product-Product Interactions:** Not applicable.
- **8.5.6 Human Carcinogenicity**

Reviewer comment(s)

Myelodysplastic syndrome (MDS)
Out of the 8 subjects who developed MDS, 7 received lisocabtagene maraleucel in Study 017001 after failure of at least 2 prior lines of therapy.

- *7/268 (2.6%) of subjects, who received lisocabtagene maraleucel after failure of at least 2 lines of systemic therapy in Study 017001 developed MDS*
- *1/150 (0.6%) of subjects who received lisocabtagene maraleucel after failure of first-line chemoimmunotherapy in Study 017006 and Study BCM-003 (Arm A).*
- *1/91 (1%) of subjects who did not receive lisocabtagene maraleucel but received standard therapy after failure of first-line chemoimmunotherapy in Study BCM-003, (Arm B) developed MDS.*

Since most subjects with LBCL receive alkylating agents, those patients have a higher risk of developing MDS. Subjects who received lisocabtagene maraleucel after failure of at least two lines of standard therapy, 7/268 (2.6%) had a higher incidence of MDS compared to subjects who received lisocabtagene maraleucel after failure of first-line immunochemotherapy, 1/150 (0.6%). However, the numbers are too small to draw any conclusions. Additionally, transgene testing on bone marrow biopsies were confirmed negative for JCAR017 in 7 samples that were tested by the Applicant. Insertion site analysis was not conducted on any MDS samples as it is only conducted when transgene is detected to identify the location and frequency of vector integration sites. Therefore, the clinical review team would not recommend including MDS in the label.

- **8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No overdoses were reported for lisocabtagene maraleucel.

- **8.5.8 Immunogenicity (Safety)**

- In the lisocabtagene maraleucel arm of Study BCM-003, the prevalence (i.e., percentage of subjects with pre-existing antibodies that bind to lisocabtagene maraleucel) and incidence (percentage of subjects with treatment-induced or treatment-boosted antibodies that bind to lisocabtagene maraleucel) of anti-therapeutic antibodies (ATA) was 1.1% (1 of 89 subjects).
- In Study 017006, the incidence of ATA was 2.0% (1 of 49 subjects) and no subject (out of 51 evaluated) had pre-existing ATAs.

Reviewer comment(s)

Due to the low incidence of ATA, it is not appropriate to assess any potential relationship of ATA with efficacy, safety, or PK.

- **8.5.9 Person-to-Person Transmission, Shedding:** Not applicable.

8.6 Safety Conclusions

The safety data and key AEs are comparable across the three lisocabtagene maraleucel studies (BCM-003, 017006, and 01700). No additional safety concerns were noted from second-line therapy for LBCL.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

- **9.1.1 Human Reproduction and Pregnancy Data**

No animal studies of reproduction or developmental toxicity have been performed, lisocabtagene maraleucel and has not been studied in pregnant women.

Reviewer comment(s)

Effective contraception was required for clinical trial participation of JCAR017. For information regarding the need for contraceptive use among patients treated with cyclophosphamide and fludarabine lymphodepleting conditioning chemotherapy, please see the respective agents' prescribing information

- **9.1.2 Use During Lactation:** Not applicable.
- **9.1.3 Pediatric Use and PREA Considerations**

There are no pediatric data in the intended population. The application does not trigger PREA, as lisocabtagene maraleucel had orphan designation for the treatment of DLBCL by the time of the original BLA submission in December 2019.

- **9.1.4 Immunocompromised Patients:** Not applicable.
- **9.1.5 Geriatric Use**

Demographics
In two clinical trials of lisocabtagene maraleucel with one prior line of therapy for LBCL, 59% (89/150) of patients were 65 years of age or older; and 19% (28/150) were 75 years of age or older. No clinically important differences in safety or effectiveness of BREYANZI were observed between patients aged ≥ 65 and younger patients.

Study BCM-003
In the lisocabtagene maraleucel arm 36 (40%) were 65 years of age or older and no patient was 75 years of age or older. There were no relevant clinical differences that occurred in the safety or effectiveness of those older than 65 years compared to younger patients.

Study 017006
The Applicant investigated the safety and efficacy of lisocabtagene maraleucel as second-line therapy in the geriatric population with LBCL after failure of first-line chemoimmunotherapy in Study 017006. The study enrolled subjects who were not eligible for high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) due to age or comorbidities. Ninety percent (55/61) of subjects in Study 017006 were older than 65 years of age. The ORR of this cohort was 82% (95% CI: 69 to 91) and the CR rate was 55% (95% CI: 41 to 68). The DOR in this cohort of patients was 11.2 months (95% CI: 4.99 to NR). Those results show the potential for lisocabtagene maraleucel to provide meaningful clinical efficacy in older populations. The safety profile of Study 017006 was similar across other lisocabtagene maraleucel studies (BMC-003 and 017001) which enrolled an overall younger population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered: N/A

10. CONCLUSIONS

A. Efficacy

Study BCM-003 and Study 017006 provide substantial evidence of efficacy in support of a second-line indication for lisocabtagene maraleucel.

1. Study BCM-003

The randomized Study BCM-003 comparing lisocabtagene maraleucel to standard therapy in primary refractory and early relapsed LBCL (within 1 year of achieving CR to first-line chemoimmunotherapy) demonstrated statistically significant improvement in event free-survival (EFS). Other efficacy measures included complete response rate, progression-free survival, and overall survival.

The analysis of EFS demonstrated a significant improvement for the lisocabtagene maraleucel arm with a stratified HR of 0.34 (95% CI:0.22, 0.51) and a p- value <0.0001. The IRC-assessed complete response (CR) rate was statistically significantly higher at 66% (95% CI: 56, 76) in the lisocabtagene maraleucel arm compared to 39% (95% CI: 29, 50) in the standard therapy arm (p-value = 0.0001). The PFS also favored the lisocabtagene maraleucel arm (14.8 months; 95% CI: 6.6, NR) compared to the standard therapy arm (5.7 months; 95% CI: 3.9, 9.4). The interim OS analysis performed at 82% information level, was not statistically significant. OS tended to favor lisocabtagene maraleucel with a HR of 0.509 (95% CI: 0.258, 1.004), one-sided p-value = 0.0257

Study BCM-003 provides substantial evidence of efficacy of lisocabtagene maraleucel compared to standard therapy in patients with primary refractory and early relapsed LBCL based on consistent improvement in EFS, PFS, and CRR and supported by OS.

2. Study 017006

The efficacy of lisocabtagene maraleucel is based on CRR with durability, which was evaluated in a multicenter, open label, single-arm clinical trial in adults with relapsed or refractory LBCL after first-line of systemic chemoimmunotherapy therapy, and who were not eligible to receive HSCT due to age or comorbidities. By independent review committee (IRC)- assessment, ORR was 81% (95% CI: 69% to 90%). The lower limit of the 95% exact Clopper-Pearson confidence interval was greater than the pre-specified null hypothesis rate of 50%. The CRR was 54% according to Lugano criteria.

- Of the 49 subjects who achieved an objective response, the estimated KM rate of continued response at 6 and 12 months was 62% and 49%, respectively
- Of the 33 subjects who achieved CR, the estimated KM rate of continued response at 6, 12, and 18 months was 83%, 68%, and 60%, respectively.

The basis of FDA's conclusion of substantial evidence of effectiveness is the magnitude of benefit primarily driven by durable complete response rate.

B. Safety

Severe CRS and neurotoxicity associated with lisocabtagene maraleucel are serious and can be life-threatening and require supportive measures. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. In addition, there is the potential for insertional mutagenesis and resultant secondary malignancies. To enhance safety, the following measures are

adopted:

1. Product labelling that includes a boxed warning for CRS and NT and a dosage and administration section that conveys a treatment algorithm for CRS and NT.
2. REMS with ETASU to assure the safe use of lisocabtagene maraleucel
3. PMR study to follow recipients of the commercial product for short term and long-term toxicity.

C. Dose

- Although the planned dose in both second-line studies was 100 × 10^6 CAR+ T cells, a dose range of 90 - 110 × 10^6 CAR+ T cells (100 million +/- 10%) has been assessed to be acceptable for approval given the variability in manufacturing of a biological product, and data to support efficacy at doses lower than 100 × 10^6 and safety data with doses up to 110 × 10^6.
- The lower limit is supported by the fact that 6/7 subjects in Study 017006 who received a lower dose (64-92 x 100 × 10^6 CAR+ T cells) achieved an objective response including 3 subjects achieving complete remission. Additionally, in the 3rd and later line setting, CRs were achieve with doses as low as 50 × 10^6 in Study 017001. Therefore, the proposed lower limit of the dose range 90 x 10^6 CAR+ T cells was considered acceptable by the clinical team.
- The upper limit of the dose that was received on Study 017006 was 103 × 10^6 CAR+ T cells. However, 3 dose levels ranging between 50 - 150 x 10^6 CAR+ T cells were previously investigated in Study 017001(n=268) and the upper limit of 110 x 10^6 CAR+ T cells (dose level 2) was found to be safe and effective and was approved as the upper dose limit. Therefore, the proposed upper limit of the dose range 110 x 10^6 CAR+ T cells was considered acceptable by the clinical team.

In conclusion, the magnitude of clinical benefit observed with lisocabtagene maraleucel is the basis for recommended regular approval:

A) Because Study BCM-003 enrolled adult patients with primary refractory and early relapsed LBCL (within 1 year of first-line chemoimmunotherapy), who were also eligible to receive HDCT and HSCT, the recommended indication is restricted to adult patients with LBCL that is refractory after or that relapses within 12 months of first- line chemoimmunotherapy.
B) Study 017006 enrolled adult patients with primary refractory or relapsed (early or late relapse) LBCL after failure of first-line chemoimmunotherapy who were also not eligible for HSCT because of age or comorbidities. Therefore, the recommended indication includes patients with LBCL that is refractory or relapse before or after 12 months after first-line chemoimmunotherapy and are not eligible for HSCT due to age or comorbidities.

In summary, Study BCM-003 and Study 017006 represent two adequate and well-controlled clinical studies that provided substantial evidence of effectiveness and safety.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 69 summarizes the risk/benefit considerations for lisocabtagene maraleucel for the treatment of adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy including DLBCL, HGBL, PMBCL, and FL grade 3B.

The safety and efficacy results included in the table are derived from two studies:

- Study BCM-003, which enrolled subjects who were eligible for HSCT.
- Study 017006, which enrolled subjects who were not eligible for HSCT due to age or comorbidities.

Table 69: Benefit – Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Half of LBCL patients will have refractory or relapsed disease following first-line (1L) rituximab and anthracycline-containing chemotherapy. Salvage chemotherapy regimens produce a response rate of 29% with 26% transplant rate and a 2-year EFS rate of 17%. Patients who do not respond to salvage chemotherapy have poor outcomes.	• There is a need for effective and safe salvage therapies for patients with R/R LBCL.
Unmet Medical Need	• The standard therapy for patients with R/R LBCL after initial therapy who are candidates for HDCT and autologous HSCT is 2L salvage chemotherapy • For patients who are not eligible to receive HDCT and HSCT, there are no curative treatment options, no approved therapies.	• Patients with R/R LBCL have unmet medical needs.
Clinical Benefit	• Interim analysis of Study BCM-003 showed that lisocabtagene maraleucel provides a statistically significant and clinically meaningful improvement in EFS (HR = 0.34; 95% CI: 0.22, 0.53; p < 0.0001), CRR (66% [95% CI: 56, 76] vs 39% [95% CI: 29, 50]; p < 0.0001), and PFS (HR = 0.41; 95% CI: 0.25, 0.66; p = 0.0001) compared to standard therapy in transplant-eligible subjects with LBCL who have refractory disease or relapsed within 12 months of CR to initial therapy. The treatment effect was consistent across major subgroups. • The efficacy of lisocabtagene maraleucel as 2L	• Based on the improvement in EFS, PFS, and CR rate in a randomized phase 3 study, lisocabtagene maraleucel has demonstrated meaningful clinical benefit compared to standard therapy in patients with R/R LBCL as 2L treatment. These data are restricted to patients with primary refractory LBCL or relapse within 12 months of CR to first-line chemoimmunotherapy. • Based on CR rate and DOR, lisocabtagene maraleucel demonstrated meaningful clinical activity as 2L treatment in patients with R/R LBCL who are transplant-ineligible due to age or comorbidities. • As seen in the third- and later-line setting, durable remissions with lisocabtagene maraleucel in the second-line setting primarily occur in patients who achieve CR.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	therapy is supported by Study 017006 which, in patients considered ineligible for HSCT, produced an ORR of 81% (95% CI: 69, 90), CRR of 54% (95% CI: 41, 67), and median DOR of 11.2 months in 61 of 74 subjects who were able to receive planned therapy. Among the 33 subjects who achieved CR, the median DOR was not reached (NR) (95% CI: 11.2 to NR) at the time of the analysis. By intention-to-treat analysis, the ORR was 68% and CRR was 46% (95% CI: 34, 58).	
Risk	• Major AEs associated with lisocabtagene maraleucel were cytokine release syndrome, neurologic toxicities, prolonged cytopenias, infectious complications, and hypogammaglobulinemia.	• Overall, the safety events reported in the Study BCM-003 and Study 017006 populations were consistent with those previously observed in 3L+ LBCL and manageable with established guidelines.
Risk Management	• The most substantial risks of lisocabtagene maraleucel are CRS and neurologic toxicity. These were mitigated in the clinical trials by careful site selection and training of investigators. • There are theoretical risks of secondary malignancy in this genetically modified immunotherapy based on the potential for replication competent retrovirus due to the retrovirus and insertional mutagenesis.	• Pharmacovigilance on postmarketing AE reports will evaluate any emergent safety issue and evaluate the postmarketing safety profile of lisocabtagene maraleucel. • Risk minimization via the product label will include the current management guideline for AEs (as stated in the lisocabtagene maraleucel USPI). • A Medication Guide will be available for patient communication on important safety information associated with lisocabtagene maraleucel and the importance of notifying their healthcare providers for the timely management of potential adverse reactions. In addition, BMS will continue to make available the safety educational tools to help healthcare providers and their patients on the appropriate use of lisocabtagene maraleucel in the 2L+ LBCL setting.

11.2 Risk-Benefit Summary and Assessment

The totality of the data from Studies BCM-003 and 017006 demonstrate a favorable benefit/risk profile for lisocabtagene maraleucel as second-line treatment for selected patients with R/R LBCL:

For patients who are considered candidates for transplant, data from Study BCM-003 indicate that lisocabtagene maraleucel represents a viable treatment option compared to standard therapy with salvage immunochemotherapy followed by HDCT and HSCT.

In patients who are transplant ineligible for reasons including advanced age, poor performance status, and/or comorbidities, Study 017006 demonstrates clinically meaningful efficacy of lisocabtagene maraleucel in a patient population with limited treatment options.

The risks of lisocabtagene maraleucel are associated with its mechanism of action and with the toxicities of the lymphodepleting regimen. CRS and neurotoxicity can be life-threatening or fatal. Hypogammaglobulinemia can persist for months and requires monitoring and potential intervention. However, the risks can be managed adequately with appropriate risk mitigation strategies in place. Safety results from Study 017006 and BCM-003 demonstrated an acceptable toxicity profile for lisocabtagene maraleucel in the second-line setting.

Overall, lisocabtagene maraleucel demonstrates a favorable benefit/risk profile in selected patients with R/R LBCL who are candidates for HSCT, as well as patients who are not eligible for HSCT due to comorbidities or age.

11.3 Discussion of Regulatory Options

Accelerated approval and regular approval are considerations for the outcomes in Studies BCM-003 and 017006. Any approval requires substantial evidence of effectiveness coupled with an acceptable safety profile and a favorable benefit/risk determination. Whereas regular approval requires demonstration of direct clinical benefit, accelerated approval requires demonstration of a positive effect on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit. To meet accelerated approval criteria, the product must also constitute an improvement over available therapies, with available therapies being determined at the time of regulatory action. Key elements of effectiveness or potential clinical benefit are magnitude and persistence of response. Demonstration of a clinically and statistically significant improvement in PFS or EFS, without an improvement in OS, may support either an accelerated approval or regular approval.

Data from the submitted studies demonstrate a clinically significant degree of efficacy after treatment with lisocabtagene maraleucel in an adequate number of subjects with LBCL who had primary refractory disease or relapse after first-line chemoimmunotherapy. The magnitude of clinical benefit demonstrated with lisocabtagene maraleucel on the following tumor-based outcomes supports regular approval: Study BCM-003 demonstrates clinical benefit through clinically meaningful improvements in EFS and PFS (as well as CR rate), while Study 017006 demonstrates clinically significant CR rates and the potential for durable CRs in a difficult-to-treat patient population having very limited if any satisfactory treatment options. In Study BCM-003, although the interim OS analysis did not reach statistical significance, the results tended to favor the lisocabtagene maraleucel arm.

The safety profile of lisocabtagene maraleucel warrants continuation of REMS with ETASU to ensure close medical monitoring and appropriate treatment of the unique adverse events, particularly of CRS and neurotoxicity. There are additional long-term safety concerns due to the use of a lentiviral vector. We have asked the Applicant to comply with an observational PMR study for short- and long-term toxicities. Additionally, the label will describe the risks and risk mitigation strategies for CRS and neurotoxicity, including a requirement to monitor patients at the certified healthcare facility frequently following infusion of lisocabtagene maraleucel.

The totality of the data from Study BCM-003 and 017006 demonstrates a favorable benefit-risk profile for lisocabtagene maraleucel as second-line treatment for selected patients with LBCL. These data support the expanded indications for lisocabtagene maraleucel specified in Section 11.4 and Section 11.5 below.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends regular approval of lisocabtagene maraleucel under an ETASU REMS for the treatment of adult patients with large B-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; 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.

Please refer to Section 11.5 for the LOU statement.

11.5 Labeling Review and Recommendations

The following are the major changes in the Applicant's proposed labeling for lisocabtagene maraleucel based on this review:

Indication

The clinical review team's recommended indication differs from the Applicant's proposed indication. The following indication statements integrate the original and new indications as represented in the draft USPI. The Applicant proposed a broad indication after failure of first-line therapy in transplant-eligible patients; however there are no data to support this indication in transplant-eligible patients who relapse >12 months after first-line therapy.

Applicant's proposed indication: 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:

- after failure of first-line therapy in patients who are candidates for hematopoietic stem cell transplant (HSCT); or
- with relapsed or refractory disease in patients for whom HSCT is not intended; or
- with relapsed or refractory disease after two or more lines of systemic therapy.

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

Recommended indication: Treatment of adult patients with large B-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; 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; or
- relapsed or refractory disease after two or more lines of systemic therapy

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

Dosage and administration

Change to the dosage; two separate doses, reflecting the new and original indications, will be necessary:

- For one prior line: a dose range of 90 -110 × 10^6 CAR+ T cells.
- For two or more prior lines of therapy: retain the 50-110 x 10^6 CAR+ T cells as already approved.

In contrast, the Applicant proposed "a target dose of 100 × 10^6 CAR+ T cells" for all indications, including the originally approved indication.

Safety

- Inclusion of all 418 subjects with diagnosis of R/R LBCL who received lisocabtagene maraleucel on studies (017001, BCM-003 and 017006) into the safety population in the Warnings and Precautions, including a new integrated analysis of CRS and neurotoxicity rates, time course, and presenting symptoms
- Other updates to the Warnings and Precautions sections regarding serious infections, prolonged cytopenias, and hypogammaglobulinemia, including:
  - New recommendation to consider HBV reactivation prophylaxis in HBV+ individuals
- Remove pooled presentation of safety in Study BCM-003 and Study 017006 in Section 6, instead describing the studies individually
- Update the rates of adverse reactions according to FDA's review and FDA grouped terms
- Clarify that the Study 017006 population, although transplant-ineligible, must meet criteria for CAR-T cell therapy
- Revise table of treatment-emergent laboratory abnormalities to use the number of patients with a baseline grade and at least one post-baseline grade, rather than the total number in the safety population, as the denominator

Efficacy

- Revise the descriptions of Study BCM-003 and Study 017006 for a streamlined presentation of study design and key results

- Study BCM-003:
  - Remove HR for OS and p-value implying statistical significance that was not met.
  - Describe difference in DOR according to best overall response.
- Study 017006 efficacy tables:
  - Add response rates in the leukapheresed (ITT) population, alongside those of the primary efficacy population.
  - Add point estimates for DOR rates according to best overall response
  - Remove the Applicant's proposed PFS, EFS, and OS data for this single-arm trial.

11.6 Recommendations on Postmarketing Actions

The Applicant is conducting a post-marketing registry study which we are considering a PMR. This study is observational and focuses on short-term toxicity, documenting adverse events, and long-term follow-up for evaluation of secondary malignancies. The plan is to enroll approximately 1500 patients and follow each patient for 15 years.

The Applicant submitted minor modification to the exiting REMS ETASU with focus on communication plan and medication guide. We determined in consultation with the OBPV and CDER DRISK that a REMS with ETASU is the most appropriate approach. The focus of the REMS ETASU is site preparation, patient education, and assessment of risk mitigation strategies on the recognition and treatment of CRS and neurotoxicity.

The REMS ETASU should be reviewed, approved, and implemented by the Applicant at participating treatment sites prior to the distribution of lisocabtagene maraleucel to the site. See Section 4.6 Pharmacovigilance for specific details of the REMS ETASU.

12. REVIEWERS' SIGNATORY

Helkha Peredo-Pinto, MD MPH

Clinical Reviewer

Mona Elmacken, MD

Clinical Reviewer

Yvette Kasamon, MD

Oncology Center of Excellence (OCE), Cross-center Clinical Team Leader

13. ONCOLOGY CENTER OF EXCELLENCE (OCE) SIGNATORY

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

Marc Theoret, MD, Deputy Director, OCE:

X

14. DIVISION DIRECTOR (DCEPT) SIGNATORY

The Office of Tissues and Advanced Therapies (OTAT) concurs with the Clinical team and OCE recommendation.

The applicant has provided substantial evidence of effectiveness and safety from two adequate, well-controlled clinical studies, to support regular approval of lisocabtagene maraleucel for the treatment of adult patients with large B-cell lymphoma (LBCL) who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; 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.

For Tejashri Purohit-Sheth, MD, Director, DCEPT:

X

APPENDIX

- **Appendix 1. FDA Grouped Terms**

Grouped Terms	Preferred Terms
Abdominal pain	abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
Anxiety	anxiety, nervousness, panic attack, procedural anxiety.
Aphasia	aphasia, disorganized speech, dysarthria, dysphemia, dysphonia, speech disorder, slow speech.
Ataxia	ataxia, balance disorder, coordination abnormal, dysmetria, dyskinesia, gait disturbance, hand-eye coordination impaired.
Bacterial infection	high-level group term.
Cardiac Arrhythmias	high-level group term.
Cardiac failure	cardiac failure acute, cardiomyopathy.
Chest pain	chest pain, chest discomfort, angina pectoris.
Coagulopathy	blood fibrinogen decreased, coagulopathy, hypofibrinogenemia, international normalized ratio increased.
Eye disorder	conjunctivitis, eye irritation, eye swelling, ocular hyperemia.
Cough	cough, productive cough, upper-airway cough syndrome.
Delirium	agitation, delirium, delusion, disorientation, hallucination; hallucination, visual; irritability, restlessness.
Depression	anhedonia, depression, decreased interest, depressed mood, flat affect, suicidal ideation.
Dizziness	dizziness, dizziness postural presyncope, syncope, vertigo.
Dyspnea	acute respiratory distress syndrome, acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, tachypnoea, wheezing.
Ecchymosis	all terms containing “ecchymosis”, “bruise” or “contusion”; bruising.
Edema	ascites, fluid overload, fluid retention, generalized oedema, hypervolemia, oedema, localized oedema, oedema peripheral, peripheral swelling, pleural effusion, pulmonary congestion, pulmonary oedema, swelling.
Encephalopathy	amnesia, apraxia, bradyphrenia, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, dyscalculia, encephalopathy, hypersomnia, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, somnolence. EXCLUDED: dysphagia.
Fatigue	asthenia, fatigue, malaise.

Grouped Terms	Preferred Terms
Fever	fever, pyrexia.
Fungal infection	high-level group term.
Gastrointestinal hemorrhage	gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematochezia, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melaena, occult blood positive, rectal hemorrhage, upper gastrointestinal hemorrhage.
Headache	headache, head discomfort, migraine, migraine with aura, sinus headache.
Hemorrhage	all terms containing “hemorrhage” or “hemorrhagic”, epistaxis, hematoma, hematuria.
Hypotension	hypotension, orthostatic hypotension.
Hypoxia	hypoxia, oxygen saturation decreased.
Infections - pathogen unspecified	high-level group term.
Insomnia	insomnia, sleep disorder.
Motor dysfunction	fine motor skill dysfunction, muscle spasms, muscular weakness, eyelid ptosis, motor dysfunction, myoclonus, muscle rigidity, muscle spasticity, muscle tightness, muscle twitching.
Musculoskeletal pain	arthralgia, back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, pain in extremity, spinal pain.
Neuropathy peripheral	neuropathy peripheral, paresthesia, hypoesthesia, hyperesthesia, peripheral sensory neuropathy, sciatica, neuralgia, sensory loss, meralgia paraesthetica, radiculopathy.
Neutropenia	neutropenia, neutrophil count decreased*
Oral pain	oral discomfort, oral dysesthesia, oropharyngeal pain.
Paresis	facial paralysis, facial paresis, hemiparesis, hemiplegia, diplegia, paresis, VII nerve paralysis, peroneal nerve palsy, gaze palsy.
Pneumonia	lung infection, lung consolidation, all terms containing “pneumonia” including organizing pneumonia.
Rash	all terms containing “rash” or “dermatitis", erythema multiforme, urticaria. EXCLUDED: erythema, catheter site erythema, erythema nodosum.
Reflexes abnormal	reflexes abnormal, hyporeflexia.
Renal failure	acute kidney injury, blood creatinine increased, renal failure, renal injury, chronic kidney disease.
Seizure	seizure, status epilepticus.

Grouped Terms	Preferred Terms
Sepsis	all terms containing "sepsis" or "bacteremia", septic shock
Supraventricular arrhythmia	high-level term.
Tachycardia	atrial fibrillation, atrial flutter, sinus tachycardia, tachycardia, heart rate increased.
Taste disorder	dysgeusia, taste disorder.
Thrombosis	all terms containing "thrombosis" or "embolism". EXCLUDED: thrombotic thrombocytopenic purpura.
Tremor	resting tremor, tremor, essential tremor.
Upper respiratory tract infection	laryngitis, nasal congestion, nasopharyngitis, paranasal sinus hypersecretion, pharyngitis, rhinitis, rhinorrhea, rhinovirus infection, sinusitis, upper respiratory tract congestion, upper respiratory tract infection.
Urinary tract infection	all terms containing "urinary tract infection", cystitis, urosepsis.
Viral infection	high-level group term.
Vision blurred	vision blurred, visual impairment, vitreous floaters.
Xerosis	dry eye, dry skin, dry mouth.

* Other laboratory terms were defined similarly

- **Appendix 2. Financial Disclosures**

Financial disclosures for Study BMC-003

Covered clinical study (BCM-003): TRANSFORM		
Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 853		
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): 9		
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: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in 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)

Financial disclosures for Study 017006

Covered clinical study (017006): PILOT		
Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 307		
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: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in 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)

Reviewer comment(s)

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

*****Do Not Change Anything Below This Line*****