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Application Type	Efficacy supplement
STN	125714.90
CBER Received Date	Dec 23, 2021
PDUFA Goal Date	June 24, 2022
Division / Office	DCGT/OTAT
Committee Chair	Helkha Peredo-Pinto
Clinical Reviewer(s)	Helkha Peredo-Pinto, Mona Elmacken
Project Manager	Niloofar Kennedy
Priority Review	Yes
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, PhD Team Leader, FDA/CBER/OBE/DB/TEB1
	Boguang Zhen, PhD Branch Chief, FDA/CBER/OBE/DB/TEB1
Applicant	Juno Therapeutics, Inc. a Bristol-Myers Squibb
Established Name	Lisocabtagene Maraleucel
(Proposed) Trade Name	Breyanzi (JCAR017)
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Formulation(s), including Adjuvants, etc	75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1, and 1% (v/v) of 25% albumin (human)
Dosage Form(s) and Route(s) of Administration	intravenous infusion
Dosing Regimen	A single dose of 100×10^6 CAR+ viable T cells
Indication(s) and Intended Population(s)	For the treatment of adult patients with relapsed or refractory large B-cell lymphoma

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GLOSSARY

Abbreviation	Definition
2L	Second-line
3L+	Third-line or later
AESI	Adverse event of Special Interest
BLA	Biologics Licensure Application
BOR	Best overall response
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HDCT	High-dose chemotherapy
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IRC	Independent Review Committee
ITT	Intent-to-treat
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LDC	Lymphodepleting chemotherapy
Liso-cel	Lisocabtagene Maraleucel
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NR	Not reached
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
R/R	Relapsed or refractory
sAAIPI	Secondary age-adjusted international prognostic index
SAE	Serious adverse event
SAP	Statistical analysis plan
sBLA	Supplemental BLA
SD	Stable Disease
SOC	Standard of care
STD	Standard deviation
US	United States

1. EXECUTIVE SUMMARY

BREYANZI is a CD19-directed genetically modified autologous cellular immunotherapy. It was originally approved by the United States (US) Food and Drug Administration (FDA) on February 05, 2021, for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy (Biologics License Application [BLA] 125714/0). In this efficacy supplement, the applicant seeks labeling change to remove the "after two or more lines of systemic therapy" from the indication and the new proposed indication is adult patients with R/R LBCL.

The primary source of evidence to support the efficacy and safety of the proposed product comes from two studies: BCM-003 and 017006.

Study BCM-003 was a randomized, open-label, multicenter study in adult subjects that were R/R after first-line therapy for LBCL and eligible for high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (HSCT). The primary endpoint was event-free survival (EFS) determined by Independent Review Committee (IRC)-FDA algorithm. One hundred and eighty-four patients were randomized in a 1:1 ratio to receive Lisocabtagene Maraleucel (liso-cel) or Standard of Care (SOC) therapy (92 patients in each arm). The median EFS was 9.5 months (95% CI: 5.8, Not Reached [NR]) for the liso-cel arm and 2.4 months (95% CI: 2.2, 4.6) for the SOC, with a stratified hazard ratio of 0.404 (95% CI: 0.267, 0.612) in favor of liso-cel, and a one-sided p-value<0.0001 based on the stratified Cox proportional-hazards (Cox-PH) regression model. The CR rate was 66.3% (95% CI: 55.7%, 75.8%) for the liso-cel arm and 39.1% (95% CI: 29.1%, 49.9%) for the SOC, with a one-sided p-value = 0.0001 based on the stratified Cochran-Mantel-Haenszel (CMH) test. The median PFS was 11.7 months (95% CI: 6.1, NR) for the liso-cel arm and 5.6 months (95% CI: 3.1, 8.6) for the SOC, with a stratified hazard ratio of 0.465 (95% CI: 0.296, 0.730) in favor of liso-cel, and a one-sided p-value = 0.0004 based on the stratified Cox-PH model.

Study 017006 was a single-arm, open-label, multicenter study in adult subjects that were R/R after first-line immunochemotherapy for LBCL and ineligible for HDCT and HSCT. Sixty-one subjects were received liso-cel and the primary endpoint was overall response rate (ORR) assessed by IRC-FDA algorithm. ORR as assessed by the IRC-FDA algorithm was 78.7% (48/61; 95% CI: 66.3%, 88.1%) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 66.3% which was above the pre-specified null hypothesis rate of 50%. Thirty-three (54.1%) subjects had a best response of CR, and 15 (24.6%) subjects had a best response of partial response (PR). The median duration of response (DOR) was 11.2 months (95% CI: 5.8, NR) for all responders. The median DOR for the partial responders was 2.0 months (95% CI: 1.5, 3.5) and for complete responders, was 21.7 month (95% CI: 12.1, NR).

Both Study BCM-003 and Study 017006 successfully rejected the null hypotheses on the pre-specified primary endpoints. Statistically significant improvements are also observed in favor of the liso-cel arm for a number of other endpoints. Hence, these statistical

analysis results provide sufficient evidence to support the safety and effectiveness of BREYANZI for the proposed indication in this BLA efficacy supplement.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Non-Hodgkin lymphomas are the seventh most common cancer in the US, accounting for 4.3% of all new cases, and 3.4% of all cancer-related deaths in 2021. Based on 2016 to 2018 data, it is estimated that 2.1% of males and females will be diagnosed with Non-Hodgkin lymphoma (NHL) during their lifetime. Based on 2011-2017 data, the percentage of patients diagnosed with NHL expected to survive for 5 years was 73%. Estimates for 2021 indicate that approximately 81,560 new cases of NHL will be diagnosed, and an estimated 20,720 patients will succumb to the disease in the US[1]. In the US, about 80% to 85% of NHL cases are categorized as B-cell lymphomas. The most common B-cell NHL is diffuse large B-cell lymphoma (DLBCL), accounting for 30% to 40% of all cases[2].

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

Currently available FDA approved therapies for the treatment of second-line (2L) LBCL include Monjuvi (accelerated approval) with an ORR of 55% (95% CI: 43%, 67%) and Keytruda (accelerated approval) with an ORR of 45% (95% CI: 32%, 60%). Keytruda is approved only for patients with refractory primary mediastinal B-cell lymphoma (PMBCL) or with relapsed PMBCL after two or more lines of therapy, with refractory PMBCL representing a small proportion of 2L LBCL patients.

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

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this supplemental BLA (sBLA).

Table 1. Summary of major pre- and post-submission regulatory activities

Date	Milestone
05/29/2015	IND 16506 submission
04/27/2016	Orphan designation granted for the treatment of DLBCL
12/15/2016	Breakthrough designation granted for the treatment of R/R aggressive large B-cell NHL
09/18/2017	Original protocol 017006 submitted
10/20/2017	RMAT designation granted for the treatment of R/R aggressive large B-cell NHL
04/25/2018	Original protocol BCM-003 submitted
02/05/2021	Original BLA 125714.0 was approved
10/22/2021	sBLA 125715.90 pre-BLA meeting
12/23/2021	sBLA 125714.90 submission
02/21/2021	sBLA 125714.90 filed. Filing letter issued to the applicant
06/24/2022	sBLA 125714.90 PDUFA action due date

(Source: Clinical Overview Table 1.4-1, p.29; FDA statistical reviewer's summary)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Study BCM-003 and 017006. These two studies are the focus of this review memo.

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

The basis of this statistical memo includes the review of clinical study reports and data sets submitted in modules 2 and 5 of sBLA 125714/90.0

5.3 Table of Studies/Clinical Trials

The totality of the safety profile in 543 subjects with R/R LBCL treated with liso-cel were provided based on Study BCM-003 and 017006, and 3 ongoing studies in 2L and third-line or later (3L+) LBCL. Table 2 summarizes the 5 studies included in the sBLA submission. Results from Study BCM-003 and Study 017006 formed the primary evidence of safety and efficacy of liso-cel for this sBLA application, which are summarized in the following sections, respectively.

Table 2. Studies in the sBLA application

Study code	Study population	Study design	# Subjects treated	Data cutoff date
BCM-003 (pivotal)	Adults with 2L TE R/R LBCL who are candidates for transplant	Phase 3 randomized, open-label, parallel group, controlled monotherapy	89*	Mar 08, 2021
017006 (pivotal)	Adults with 2L TNE R/R LBCL for whom HSCT is not intended	Phase 2 open-label, single-arm liso-cel monotherapy	61	May 28, 2021
017001	Adult 3L+ R/R LBCL (DLBCL Cohort)	Phase 1 open-label, single-arm liso-cel monotherapy	268	Apr 12, 2019
JCAR017-BCM-001	Adult 2L R/R TNE LBCL (Cohort 2) Adult 3L+ R/R LBCL (Cohort 1, 7)	Phase 2 open-label, single-arm, multicohort liso-cel monotherapy	54	Jan 04, 2021
017007	Adult 3L+ R/R LBCL	Phase 2 open-label, single-arm monotherapy, outpatient administration	71	Mar 03, 2021

* N=184 randomized (92 per arm, of which 89 treated liso-cel)
TE=transplant eligible; TNE=transplant non-eligible.
(Source: Clinical Overview Table 1.3-1, p.17; FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study # BCM-003

6.1.1 Objectives

Primary:
To compare the efficacy in subjects treated with liso-cel versus subjects treated according to SOC defined as EFS.

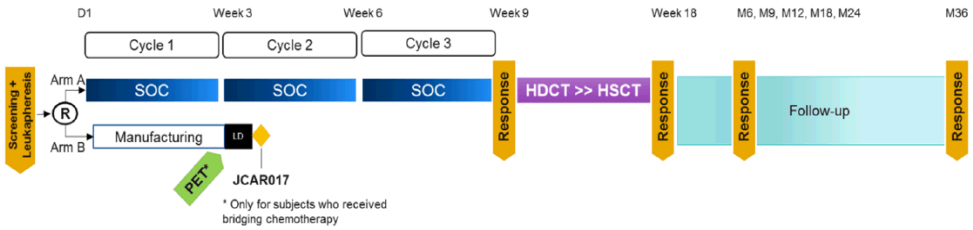
Key secondary:
To compare the efficacy in subjects treated with liso-cel versus subjects treated according to SOC defined as CR rate, PFS and OS.

6.1.2 Design Overview

Study BCM-003 was a randomized, open-label, parallel-group, multi-center Phase 3 study to demonstrate the efficacy and safety of liso-cel versus SOC (salvage immunochemotherapy followed by HDCT and HSCT) in subjects with LBCL who are refractory to or have relapsed within 12 months from first-line therapy and are eligible for HDCT and autologous HSCT.

Subjects were randomized to receive either SOC or liso-cel. Randomization was stratified by response to first-line therapy (refractory defined as stable disease [SD], progressive disease [PD], PR or CR lasting < 3 months versus relapsed defined as CR lasting 3 to 12 months), and secondary age-adjusted international prognostic index (sAAIPI) (0 to 1 versus 2 to 3) at the screening. All subjects randomized to the SOC were to receive 3 cycles of SOC salvage therapy (i.e., R-DHAP, R-ICE, or R-GDP) as per physician's choice. Subjects responding to SOC (CR or PR) after 3 cycles of therapy were to proceed to HDCT and autologous HSCT. Subjects randomized to the liso-cel arm were to receive lymphodepleting chemotherapy (LDC) consisting of fludarabine and cyclophosphamide for 3 days followed by liso-cel infusion 2 to 7 days after completion of LDC. In the liso-cel arm, bridging chemotherapy with one of the protocol-defined SOC salvage regimens was allowed for disease control while liso-cel was being manufactured if deemed necessary by the investigator. Figure 1 below gives the overview of Study BCM-003 design schematic.

Figure 1. Study BCM-003 design schematic



(Source: Summary of Clinical Efficacy Figure 1.1.1-1, p.16)

If requested by the investigator, subjects in SOC were allowed to receive liso-cel upon central confirmation by the IRC of one of the following criteria:

- Failure to achieve CR or PR by 9 weeks post-randomization
- Progression at any time
- Need to start a new antineoplastic therapy due to efficacy concerns (absence of CR) after 18 weeks post-randomization

6.1.3 Population

Key elements of eligibility criteria for Study BCM-003 are listed below.

- Eligible subjects were ≥ 18 years and ≤ 75 years of age with R/R LBCL.
- Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 at screening.
- The trial excluded subjects who were not eligible for HSCT and those who had received treatment with any prior gene therapy product or CD19-targeted therapy.
- The trial excluded subjects with a history or presence of clinically relevant central nervous system pathology.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A single liso-cel dose of 100×10^6 CAR+ T cells.

6.1.6 Sites and Centers

Forty-eight (48) study sites globally including 26 study sites in the US.

6.1.7 Surveillance/Monitoring

An independent, external statistical group was responsible of performing the interim analyses. The Data Safety Monitoring Board (DSMB) was responsible for reviewing such analyses and providing recommendations to the applicant. The study team remained blinded to study results until DSMB review of the 80% information fraction results was completed.

6.1.8 Endpoints and Criteria for Study Success

In Study BCM-003, the primary endpoint 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 3 cycles of SOC for SOC and 5 weeks after liso-cel infusion for liso-cel arm) or start of new antineoplastic therapy due to efficacy concerns (the decision was made by the primary oncologist who was treating the patient), whichever comes first.

The study protocol also included several key secondary efficacy endpoints:

a. CR rate, defined as the percentage of subjects achieving a CR.
b. PFS, defined as the time from randomization to PD or death from any cause, whichever occurs first.
c. OS, defined as the time from randomization to time of death due to any cause.

If the null hypothesis was rejected for the primary endpoint EFS, hypothesis testing on CR rate (and subsequently on PFS and OS) was to be performed hierarchically.
Note: In the applicant's submission, the response was assessed by IRC based on the Lugano 2014 criteria. However, per clinical review team request, we used the IRC-FDA algorithm as the primary method to assess response in this memo. The response assessed by IRC was used for sensitivity analysis in the FDA review.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

Statistical hypothesis:
The analysis of the primary efficacy endpoint was performed by testing
H_0: HR $\geq$ 1 versus H_a: HR < 1, where HR is the hazard ratio of liso-cel arm versus SOC.

Analysis populations:

- *Intention-to-Treat (ITT) Analysis Set* included all subjects randomized to a treatment arm.
- *Safety Analysis Set* included all subjects who take at least one dose of study treatment.
- *Cross over Analysis Set* included all subjects of the ITT analysis set randomized in SOC who cross over to liso-cel treatment.

Statistical methods:
Efficacy analyses were conducted on the ITT analysis set. For the primary analysis, IRC-FDA assessment of disease status would be used.

Primary endpoint
The primary efficacy endpoint, EFS, was analyzed with a stratified (by randomization stratification factors) Cox-PH regression model. In addition, Kaplan-Meier (KM) curves were presented, and KM estimates and 2-sided 95% confidence intervals were calculated.

Key secondary endpoints

- CR rate: An exact binomial 2-sided 95% confidence interval was generated for the estimated CR rate and best response rates for each treatment arm. Conditional on demonstrating a statistically significant improvement in EFS, testing the significance of CR rate was performed with a CMH test stratified by randomization stratification factors for the common odds ratio of response.
- PFS, OS and DOR: The same analysis methods applied to EFS were applied to the analysis of PFS, OS and DOR.

Note: Although DOR was not key secondary endpoint proposed by the applicant, DOR was analyzed in the efficacy analysis section per requested by the clinical review team.

Interim analyses:
The protocol and statistical analysis plan (SAP) v1.2 originally included two interim analyses, one for futility and one for efficacy. However, following the Agency review of

the interim analysis (IA) for efficacy at 60% information fraction, one more IA for efficacy at 80% information fraction was added in the SAP addendum v1.1.

The IA for futility was performed when ~30 evaluable subjects (~15 subjects per arm and having received the treatment) had their Week 9 response assessment or had been confirmed with disease progression prior to this timepoint. The futility stopping rule was non-binding.

The second IA was to demonstrate the superior efficacy of liso-cel versus SOC based on EFS. The pre-specified interim timing was ~60% information fraction (i.e., at ~71 EFS events), where the overall one-sided alpha level of 0.025 were to be split at the second IA and the final analysis with an efficacy boundary of 0.004 and 0.024, respectively, using the O'Brien-Fleming method. The actual timing of such interim analysis was at 63% information fraction and 75 EFS events, where the efficacy threshold was adjusted to 0.005 based on the actual number of EFS events observed.

Upon completion of the second interim analysis, the Agency indicated that the IA at 63% information fraction was not mature enough for a regulatory filing and recommended that another efficacy IA be performed at 80% information fraction (i.e., at ~96 EFS events). Thus, this additional efficacy IA took place at 82% information fraction and 98 EFS events, where the efficacy threshold was adjusted from 0.011 to 0.012 based on the actual number of EFS events observed at the time of this analysis, using the O'Brien-Fleming method. Therefore, the overall alpha level was split among the two efficacy interim analyses and the final analysis with an efficacy boundary of 0.005, 0.012 and 0.021, respectively.

Sample size and power calculation:

The following assumptions were used to determine the sample size for this study:

- a median EFS of 3 months and 5.4 months for SOC and liso-cel arm, respectively (HR=0.55)
- log-rank test was used
- one-sided alpha level of 0.025
- target power of 90%
- an expected randomization rate of up to 12 subjects per month
- a 20% dropout rate before Week 9 response assessment and a yearly dropout rate of 10% thereafter

Given the assumptions above, 120 EFS events are required. A sample size of 182 subjects was needed to be randomized and 216 subjects to be screened (assuming a screen failure rate of 15%).

Note: In the study design stage, only one efficacy IA at 60% information fraction and the final analysis were considered in the above sample size and power calculation. The second efficacy IA at 80% information fraction was recommended by the Agency when the study was ongoing, thus it was not considered in the sample size calculation. However, the efficacy boundary of final analysis does take into consideration the second efficacy interim analysis.

Subgroup analyses:
In the ITT analysis set, subgroup analyses were performed based on age, sex, race and a variety of other baseline clinical characteristics.

Missing data:
Censoring rule for EFS is in the Appendix.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 summarizes the analysis sets in Study BCM-003. Leukapheresed set included 184 subjects. All these subjects were randomized with allocation ratio of 1:1 to liso-cel arm and SOC that constituted the ITT analysis set, and 183 (99.5%) subjects received at least one dose of study treatment that constituted the safety analysis set.

Table 3. Analysis sets in Study BCM-003

Analysis set	N
Screened	232
Leukapheresed	184
ITT (Randomized)	184 (liso-cel: 92; SOC: 92)
Safety	183 (liso-cel: 92; SOC: 91)

Note: The data cut-off date is March 08, 2021, when 98 EFS events (i.e., 82% information fraction) were identified
(Source: FDA statistical reviewer's summary)

6.1.10.1.1 Demographics

Table 4 shows the demographic information for subjects in the ITT analysis set. The demographic information was generally balanced between the liso-cel arm and SOC, except for sex, SOC had more male subjects than liso-cel arm did (66.3% versus 47.8%).

Table 4. Subject demographics (ITT analysis set) in Study BCM-003

	Liso-cel, n=92	SOC, n=92	Overall, n=184
Age (years)			
Mean (STD)	58.3 (12.6)	54.2 (13.9)	56.3 (13.4)
Median (min, max)	60 (20, 74)	58 (26, 75)	59 (20, 75)
Sex, n (%)			
Female	48 (52.2%)	31 (33.7%)	79 (42.9%)
Male	44 (47.8%)	61 (66.3%)	105 (57.1%)
Race, n (%)			
White	54 (58.8%)	55 (59.8%)	109 (59.2%)
Black or African American	4 (4.3%)	3 (3.3%)	7 (3.8%)
Asian	10 (10.9%)	8 (8.7%)	18 (9.8%)
Other	2 (2.1%)	1 (1.1%)	3 (1.6%)
Missing	22 (23.9%)	25 (27.1%)	47 (25.5%)

(Source: FDA statistical reviewer's summary)

Reviewer Comment #1:
This reviewer observed that the sex was imbalanced between the liso-cel arm and SOC, thus performed the stratified Cox-PH regression model to examine the sex effect on EFS. No statistically significant relationship was detected.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline disease characteristics of subjects enrolled in Study BCM-003 are summarized in Table 5. Overall, 117 (63.6%) subjects had DLBCL and 43 (23.4%) had double hit or triple hit lymphoma. Baseline sAAIPI was 0 or 1 in 111 (60.3%) subjects and 2 or 3 in 73 (39.7%) subjects. Prior response status was refractory in 135 (73.4%) subjects and relapse in 49 (26.6%) subjects. These key baseline characteristics were generally balanced between the liso-cel arm and SOC.

Table 5. Baseline characteristics (ITT analysis set) in Study BCM-003

	Liso-cel, n=92	SOC, n=92	Overall, n=184
NHL Type, n (%)			
DLBCL	60 (65.2%)	57 (62.0%)	117 (63.6%)
FL3B	1 (1.1%)	0	1 (0.5%)
HGBL	22 (23.9%)	21 (22.8%)	43 (23.4%)
PMBCL	8 (8.7%)	10 (10.9%)	18 (9.8%)
THRBCL	1 (1.1%)	4 (4.3%)	15 (2.7%)
Time from Most Recent Relapse to Randomization (months)			
n	51	54	105
Mean (STD)	1.39 (1.02)	1.53 (1.26)	1.46 (1.15)
Median (min, max)	1.15 (0.1, 5.9)	1.12 (0.3, 7.7)	1.15 (0.1, 7.7)
ECOG score at screening, n (%)			
0	48 (52.2%)	57 (62.0%)	105 (57.1%)
1	44 (47.8%)	35 (38.0%)	79 (42.9%)
sAAIPI at screening, n (%)			
0 or 1	56 (60.9%)	55 (59.8%)	111 (60.3%)
2 or 3	36 (39.1%)	37 (40.2%)	73 (39.7%)
Prior Response Status, n (%)			
Refractory	67 (72.8%)	68 (73.9%)	135 (73.4%)
Relapse	25 (27.2%)	24 (26.1%)	49 (26.6%)
Best Response to Previous Systemic Regimen, n (%)			
CR	30 (32.6%)	28 (30.4%)	58 (31.5%)
PR	36 (39.1%)	45 (48.9%)	81 (44.0%)
SD	7 (7.6%)	5 (5.4%)	12 (6.5%)
PD	18 (19.6%)	13 (14.1%)	31 (16.8%)
Not Evaluable (NE)	1 (1.1%)	1 (1.1%)	2 (1.1%)

FL3B=follicular lymphoma grade 3B; HGBL=high-grade B-cell lymphoma with DLBCL histology; THRBCL=T-cell/histiocyte-rich large B-cell lymphoma
(Source: FDA statistical reviewer's summary)

6.1.10.1.3 Subject Disposition

At the time of the data cutoff date March 08, 2021, out of the 92 subjects who had randomized to the liso-cel arm, 89 had received the liso-cel infusion, 69 had completed the treatment period, 12 were still in the treatment period, and 11 had discontinued. Among the 11 subjects who discontinued, the most common reason was disease relapse (N = 6). Among the 92 subjects who had randomized to the SOC, 27 had completed the treatment period, 10 were still in the treatment period, and 55 had discontinued. Among the 55 subjects who discontinued, the most common reason was lack of efficacy (N=26). In the SOC, there were 50 subjects (54.3%) had approved for cross over to the liso-cel arm after IRC confirmation of a qualifying event. Among these 50 subjects, 46 subjects received the liso-cel infusion.

6.1.11 Efficacy Analyses

By the data cut-off date on March 08, 2021, 98 EFS events were identified (i.e., 82% information fraction). Therefore, in the efficacy analyses below for Study BCM-003, the null hypothesis was to be rejected if the one-sided p-value associated with the test was ≤ 0.012 calculated from the O'Brien-Fleming method.

6.1.11.1 Analyses of Primary Endpoint

Table 6 summarizes the EFS result in the ITT analysis set per IRC-FDA and IRC assessments, respectively. 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 liso-cel 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 SOC. The subjects in the liso-cel arm had substantially longer median EFS than those in the SOC. Based on the result from the stratified Cox-PH model, the liso-cel arm demonstrated a statistically significant improvement in EFS based on IRC-FDA assessment compared to the SOC: HR = 0.397 (95% CI: 0.263, 0.600); one-sided p-value < 0.0001. Similar to result of EFS assessed by IRC assessment.

Table 6. EFS result per IRC-FDA and IRC (ITT analysis set) in Study BCM-003

	IRC-FDA algorithm		IRC assessment	
	Liso-cel, n=92	SOC, n=92	Liso-cel, n=92	SOC, n=92
Number of events, n (%)	38 (41.3%)	60 (65.2%)	35 (38.0%)	63 (68.5%)
Progression	31 (33.7%)	43 (46.7%)	26 (28.3%)	39 (42.4%)
Death	2 (2.2%)	2 (2.2%)	2 (2.2%)	2 (2.2%)
Failure to achieve CR or PR by 9 Weeks post-randomization	3 (3.3%)	14 (15.2%)	4 (4.3%)	17 (18.5%)
Start a new antineoplastic therapy due to efficacy concerns	2 (2.2%)	1 (1.1%)	3 (3.3%)	5 (5.4%)
Censored, n (%)	54 (58.7%)	32 (34.8%)	57 (62.0%)	29 (31.5%)
No baseline, or no post-baseline response assessment and no death	2 (2.2%)	4 (4.3%)	2 (2.2%)	1 (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 (56.5%)	28 (30.4%)	55 (59.8%)	28 (30.4%)
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	(6.0, 11.1)	(6.0, 11.5)	(6.0, 10.6)	(6.0, 11.5)
Percentage of subjects with EFS at [c]				
6 months (95% CI)	60.1 (47.8, 70.4)	35.8 (25.2, 46.4)	63.3 (50.9, 73.4)	33.4 (23.3, 43.8)
12 months (95% CI)	42.1 (27.5, 56.0)	25.4 (15.3, 36.7)	44.5 (29.2, 58.7)	23.7 (14.3, 34.6)
24 months (95% CI)	36.1 (20.2, 52.2)	19.0 (7.9, 33.9)	38.1 (21.3, 54.8)	17.8 (7.4, 31.9)
Stratified Cox PH model (Liso-cel arm versus SOC)				
HR (95% CI)	0.397 (0.263, 0.600)		0.339 (0.223, 0.515)	
One-sided p-value	< 0.0001		< 0.0001	

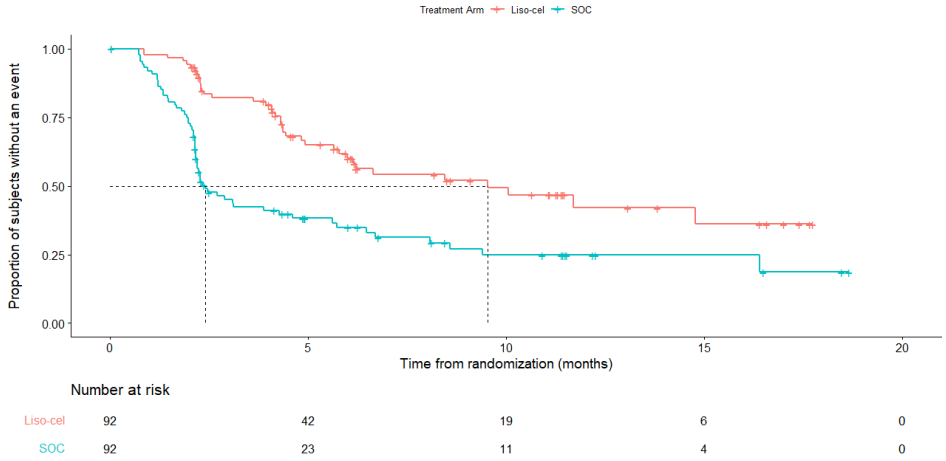
a KM product limit estimates using log-log transformation
b Reverse KM method
c CI calculated using Greenwood's formula
(Source: FDA statistical reviewer's analysis)

Reviewer Comment #2:

Starting a new antineoplastic therapy due to efficacy concerns could bias the EFS endpoint in an open-label trial as investigators might put more SOC 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 for this study, it is not necessary to conduct further analysis on the primary efficacy endpoint, EFS.

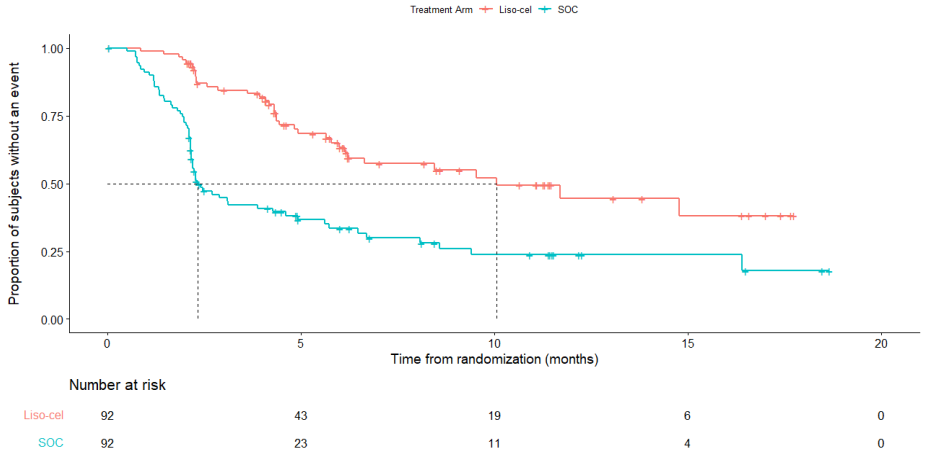
Figure 2 and 3 show KM curve of EFS per IRC-FDA algorithm and IRC assessment, respectively, in the ITT analysis set by treatment arm. The subjects in the liso-cel arm had substantially longer EFS than those in the SOC under both assessments.

Figure 2. KM curve of EFS per IRC-FDA (ITT analysis set) in Study BCM-003



(Source: FDA statistical reviewer's analysis)

Figure 3. KM curve of EFS per IRC (ITT analysis set) in Study BCM-003



(Source: FDA statistical reviewer's analysis)

Sensitivity analyses were conducted by the applicant, under various censoring rules for EFS. Results were consistent with the results of the primary analysis of EFS.

6.1.11.2 Analyses of Key Secondary Endpoints

CR rate

Table 7 summarizes the best overall response (BOR) including CR rate per IRC-FDA algorithm and IRC assessment, respectively. In the ITT analysis set, among 92 subjects in the liso-cel arm, 74 subjects (80.4%) had a BOR of CR or PR, as determined by IRC-FDA algorithm. Among the 74 responders, 59 subjects (64.1%) had a best response of CR, and 15 (16.3%) subjects had a best response of PR. Among 92 subjects in the SOC,

43 subjects (46.7%) had a BOR of CR or PR, as determined by IRC-FDA algorithm. Among the 43 responders, 36 subjects (39.1%) had a best response of CR, and 7 (7.6%) had a best response of PR. The subjects in the liso-cel arm had substantially higher ORR and CR rate than those in the SOC. Based on the result from the stratified CMH test, the liso-cel arm demonstrated a statistically significant improvement in CR rate based on IRC-FDA assessment compared to the SOC with one-sided p-value = 0.0001. Analysis of ORR including CR rate assessed by IRC results in the similar conclusion as assessed by IRC-FDA algorithm.

Table 7. BOR per IRC-FDA and IRC (ITT analysis set) in Study BCM-003

	IRC-FDA algorithm		IRC assessment	
	Liso-cel, n=92	SOC, n=92	Liso-cel, n=92	SOC, n=92
ORR (CR+PR), n (%)	74 (80.4%)	43 (46.7%)	79 (85.9%)	44 (47.8%)
95% CI	(70.9%, 88.0%)	(36.3%,57.4%)	(77.0%, 92.3%)	(37.3%, 58.5%)
CR, n (%)	59 (64.1%)	36 (39.1%)	61 (66.3%)	36 (39.1%)
95% CI	(53.5%, 73.9%)	(29.1%,49.9%)	(55.7%, 75.8%)	(29.1%,49.9%)
Stratified CMH test p-value (one-sided)	0.0001		<0.0001	
PR, n (%)	15 (16.3%)	7 (7.6%)	18 (19.6%)	8 (8.7%)
95% CI	(9.4%, 25.5%)	(3.1%,15.1%)	(12.0%, 29.1%)	(3.8%, 16.4%)
SD, n (%)	2 (2.2%)	17 (18.5%)	4 (4.3%)	21 (22.8%)
PD, n (%)	13 (14.1%)	29 (31.5%)	6 (6.5%)	24 (26.1%)
NE, n (%)	3 (3.3%)	3 (3.3%)	3 (3.3%)	3 (3.3%)

(Source: FDA statistical reviewer's analysis)

PFS

Table 8 summarizes the PFS result in the ITT analysis set per IRC-FDA and IRC assessments, respectively. For analysis of PFS per IRC-FDA algorithm, the overall median was 11.7 months with a lower 95% limit of 6.1 months and an unattainable upper limit in the liso-cel arm; and the overall median was 5.6 months with a lower 95% limit of 3.1 months and an upper limit of 8.6 months in the SOC. The subjects in the liso-cel arm had substantially longer median PFS than those in the SOC. Based on the result from the stratified Cox-PH model, the liso-cel arm demonstrated a statistically significant improvement in PFS based on IRC-FDA compared to the SOC: HR = 0.465 (95% CI: 0.296, 0.730); p-value = 0.0004. Similar to result of PFS assessed by IRC.

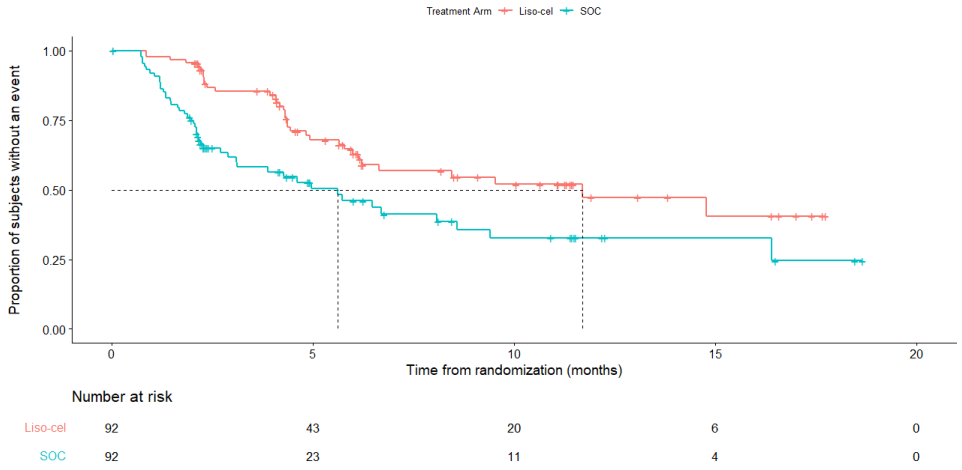
Table 8. PFS result per IRC-FDA and IRC (ITT analysis set) in Study BCM-003

	IRC-FDA algorithm		IRC assessment	
	Liso-cel, n=92	SOC, n=92	Liso-cel, n=92	SOC, 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)
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)
Percentage of subjects with PFS at				
6 months (95% CI)	62.9 (50.4, 73.0)	46.1 (33.5, 57.9)	69.4 (56.6, 79.1)	47.8 (34.6, 59.8)
12 months (95% CI)	47.3 (32.2, 61.0)	32.8 (20.0, 46.0)	52.3 (35.8, 66.4)	33.9 (20.7, 47.6)
24 months (95% CI)	40.5 (23.2, 57.2)	24.6 (10.0, 42.5)	44.9 (25.6, 62.4)	25.4 (10.3, 43.9)
Stratified Cox-PH model (Liso-cel arm versus SOC)				
HR (95% CI)	0.465 (0.296, 0.730)		0.406 (0.250, 0.659)	
One-sided p-value	0.0004		0.0001	

(Source: FDA statistical reviewer's analysis)

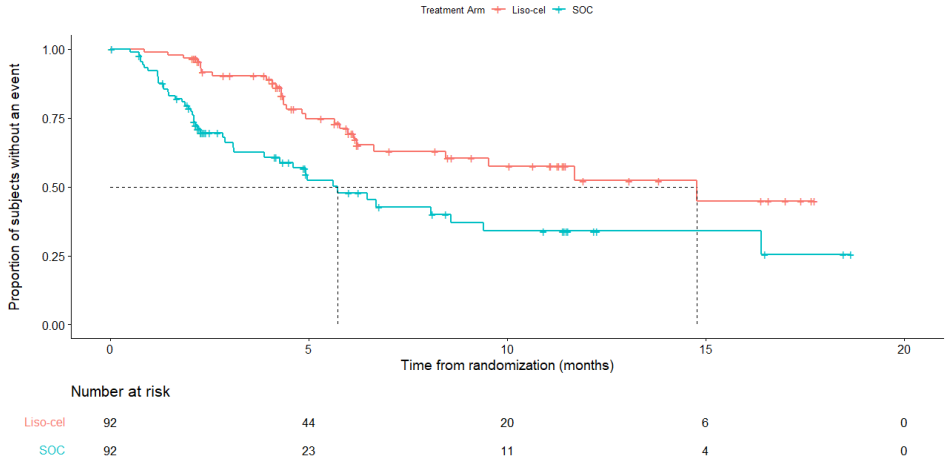
Figure 4 and 5 show KM curve of PFS per IRC-FDA and IRC assessment, respectively, in the ITT analysis set by treatment arm. The subjects in the liso-cel arm had substantially longer PFS than those in the SOC under both assessments.

Figure 4. KM curve of PFS per IRC-FDA (ITT analysis set) in Study BCM-003



(Source: FDA statistical reviewer's analysis)

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



(Source: FDA statistical reviewer's analysis)

OS

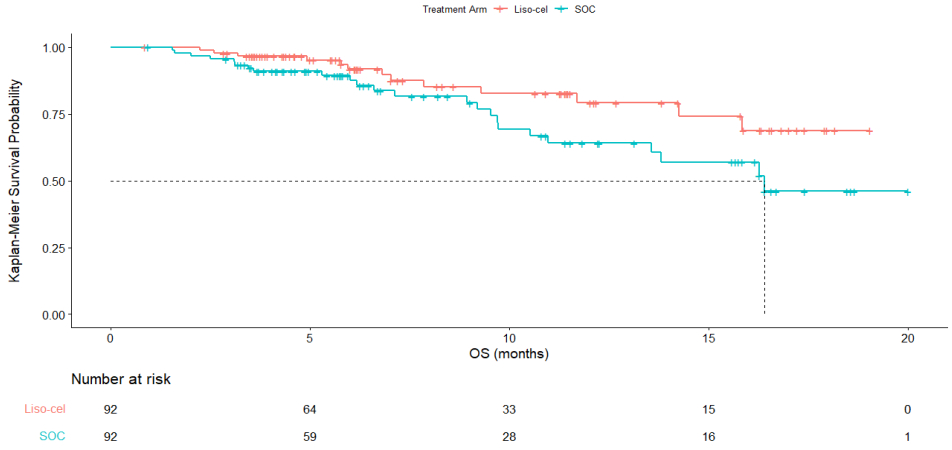
Table 9 summarizes the OS result in the ITT analysis set. The overall median was unattainable with a lower 95% limit of 15.8 months and an unattainable upper limit in the liso-cel arm; and the overall median was 16.4 months with a lower 95% limit of 11.0 months and an unattainable upper limit in the SOC. Based on the result from the stratified Cox-PH regression model, the liso-cel arm did not demonstrate a statistically significant improvement in OS compared to the SOC based on the ITT principle, although a numerical trend in favor of the liso-cel arm was observed from Figure 6: HR = 0.509 (95% CI: 0.258, 1.004); one-sided p-value = 0.0257.

Table 9. OS result (ITT analysis set) in Study BCM-003

	Liso-cel, n=92	SOC, 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)
Percentage of subjects with OS at		
6 months (95% CI)	91.8 (82.3, 96.3)	89.4 (80.6, 94.4)
12 months (95% CI)	79.1 (63.9, 88.5)	64.2 (48.8, 76.0)
24 months (95% CI)	68.9 (48.7, 82.4)	46.1 (27.3, 63.0)
Stratified Cox-PH model (Liso-cel arm versus SOC)		
HR (95% CI)	0.509 (0.258, 1.004)	
One-sided p-value	0.0257	

(Source: FDA statistical reviewer's analysis)

Figure 6. KM curve of OS (ITT analysis set) in Study BCM-003



(Source: FDA statistical reviewer's analysis)

DOR

Table 10 summarizes the DOR result in the ITT analysis set per IRC-FDA and IRC assessments, respectively. For analysis of 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 liso-cel 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 SOC. Based on the result from the stratified Cox-PH model, the liso-cel arm did not demonstrate a statistically significant improvement in DOR based on IRC-FDA assessment compared to the SOC: HR = 0.831 (0.424, 1.630); p-value = 0.295. Similar to result of DOR assessed by IRC assessment.

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

	IRC-FDA algorithm		IRC assessment	
	Liso-cel, n=92	SOC, n=92	Liso-cel, n=92	SOC, n=92
Number of subjects achieved CR or PR, n	74	43	79	44
Number of events, n (%)	21 (22.9%)	15 (16.3%)	22 (23.9%)	16 (17.4%)
Progression	18 (19.6%)	14 (15.2%)	18 (19.6%)	14 (15.2%)
Death	1 (1.1%)	1 (1.1%)	1 (1.1%)	1 (1.1%)
Start a new anti-cancer therapy due to efficacy concerns	2 (2.2%)	0	3 (3.3%)	1 (1.1%)
Censored, n (%)	53 (57.6%)	28 (30.4%)	57 (62.0%)	28 (30.4%)
No response assessment after first response and no death	12 (13.0%)	6 (6.5%)	14 (15.2%)	6 (6.5%)
No death or no PD	41 (44.6%)	22 (23.9%)	43 (46.7%)	22 (23.9%)
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)
Percentage of subjects with response duration				
≥6 months (95% CI)	64.5 (49.1, 76.2)	65.9 (46.5, 79.7)	64.1 (49.1, 75.8)	64.4 (45.4, 78.3)
≥12 months (95% CI)	57.8 (41.5, 71.1)	52.1 (31.7, 69.0)	57.5 (41.5, 70.7)	50.9 (31.0, 67.8)
≥24 months (95% CI)	49.6 (29.0, 67.2)	34.7 (8.8, 63.1)	49.3 (28.9, 66.8)	33.9 (8.7, 62.0)
Stratified Cox-PH model (Liso-cel arm versus SOC)				
HR (95% CI)	0.831 (0.424, 1.630)		0.787 (0.409, 1.514)	
One-sided p-value	0.295		0.236	

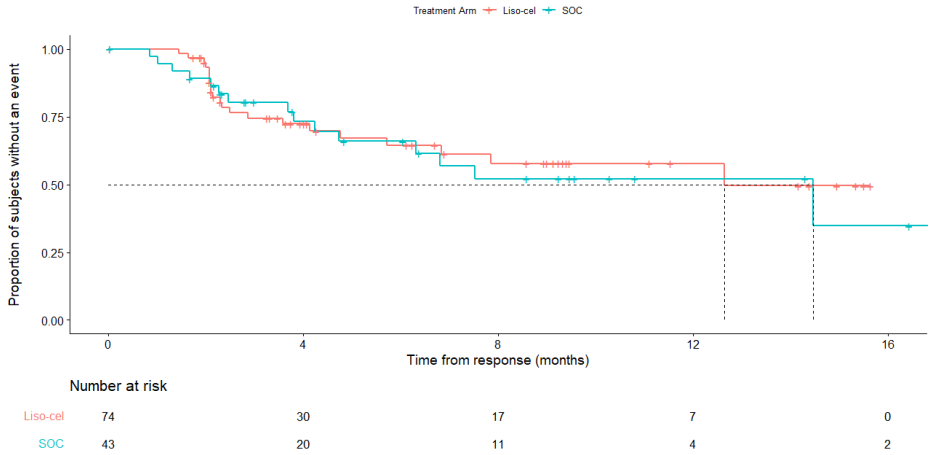
(Source: FDA statistical reviewer's analysis)

Reviewer Comment #3:

Table 10 shows that liso-cel arm had higher proportion of disease progression (19.6% versus 15.2%) and Figure 7 below shows that liso-cel arm had a smaller median DOR (12.6 month versus 14.5 month) compared with SOC. However, it is difficult to interpret the DOR results in Figure 7 as the survival curves for treatment and control overlap and cross over with each other during the course of study, violating the proportional hazards assumption. Given that, a singular measure of treatment effect, such as the median DOR or average hazard ratio, are not adequate to capture or summarize the entire treatment effect profile under the DOR endpoint. In addition, the violation of the proportional hazards assumption also makes the Cox-PH regression model less efficient to detect the difference in DOR between liso-cel and SOC arms.

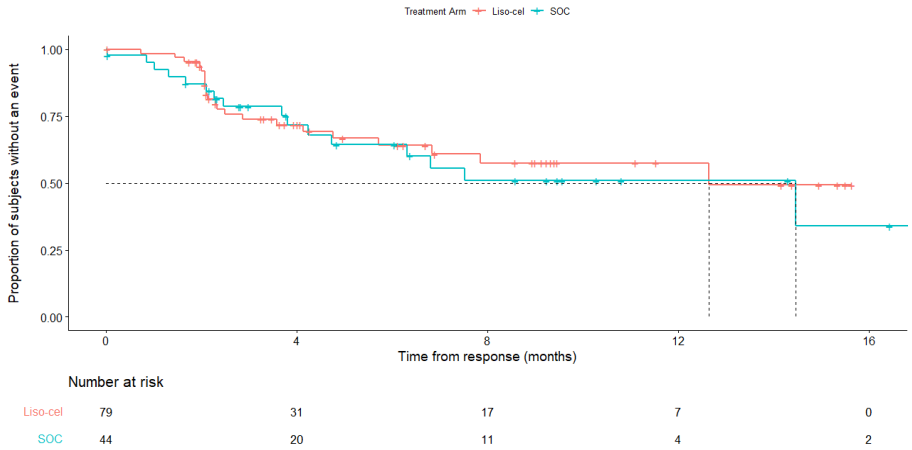
Figure 7 and 8 show KM curve of DOR per IRC-FDA algorithm and IRC assessment, respectively, in the ITT analysis set by treatment arm.

Figure 7. KM curve of DOR per IRC-FDA (ITT analysis set) in Study BCM-003



(Source: FDA statistical reviewer's analysis)

Figure 8. KM curve of DOR per IRC (ITT analysis set) in Study BCM-003

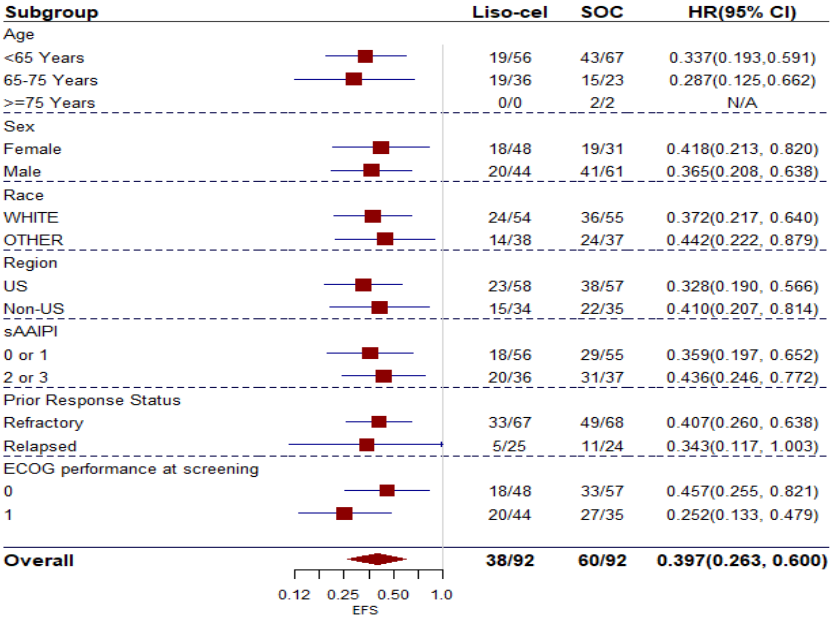


(Source: FDA statistical reviewer's analysis)

6.1.11.3 Subpopulation Analyses

Figure 9 shows the forest plot of EFS in the ITT analysis set by age group, sex, race, geographic region and a variety of other baseline clinical characteristics. The result appears to be generally consistent across subgroups.

Figure 9. Forest plot of EFS result across subgroups in Study BCM-003



(Source: FDA statistical reviewer's analysis)

6.1.12 Safety Analyses

This section briefly summarizes safety results of Study BCM-003.

6.1.12.1 Methods

Descriptive statistic was used to summarize safety data for Study BCM-003. The safety analysis set in this section included a total of 183 subjects (liso-cel arm: 92; SOC: 91) who received at least one dose of study treatment.

6.1.12.3 Deaths

Deaths reported in the study are listed in Table 11. Among 92 treated subjects in the liso-cel arm, 13 (14.1%) subjects died. Forty-four out of 91 treated subjects in the SOC did not crossover to receive liso-cel and 8 (18.2%) of them died. Forty-seven subjects in the SOC received liso-cel as a subsequent therapy and 16 (34.0%) of them died.

Table 11. Deaths reported in Study BCM-003

	No. of Subjects (%)		
Safety parameters	SOC did not crossover (N=44)	SOC post-crossover (N=47)	Liso-cel (N=92)
Death	8 (18.2)	16 (34.0)	13 (14.1)
Cause of Death Category			
Death from malignant disease under study, or complication due to malignant disease under study	4 (9.1)	9 (19.1)	7 (7.6)
Death from adverse event (not otherwise specified)	4 (9.1)	0	2 (2.2)
Other	0	3 (6.4)	3 (3.3)
Unknown	0	4 (8.5)	1 (1.1)

(Source: FDA statistical reviewer's summary; Study BCM-003 Clinical Study Report Table 35, p.173)

6.1.12.4 Nonfatal Serious Adverse Events

Table 12 summarizes the treatment-emergent non-fatal serious adverse event (SAE) reported in at least 20% of treated subjects in any grade for each treatment arm. Almost all subjects in each arm experienced at least one treatment-emergent SAE. The most frequently reported treatment-emergent SAE was neutropenia in the liso-cel arm and thrombocytopenia in the SOC.

Table 12. Treatment-emergent non-fatal SAEs reported in >= 20% of treated subjects in Study BCM-003

Safety Parameters	No. of Subjects (%)			
	SOC Arm (N = 91)		Liso-cel Arm (N = 92)	
All SAEs	**44 (48.4)**		**44 (47.8)**	
All Treatment-emergent SAEs (related to any drug)	**34 (37.4)**		**31 (33.7)**	
All-causality AEs leading to Withdrawal of any Study Drug	**4 (4.4)**		**0**	
	Any Grade	**Grade 3/4**	**Any Grade**	**Grade 3/4**
TEAEs	90 (98.9)	79 (86.8)	92 (100)	85 (92.4)
Most frequently reported AEs (≥ 20% of any grade in either treatment group)				
Neutropenia	49 (53.8)	46 (50.5)	75 (81.5)	74 (80.4)
Anaemia	58 (63.7)	45 (49.5)	58 (63.0)	45 (48.9)
Thrombocytopenia	62 (68.1)	58 (63.7)	53 (57.6)	45 (48.9)
Nausea	52 (57.1)	3 (3.3)	49 (53.3)	3 (3.3)
Fatigue	35 (38.5)	2 (2.2)	36 (39.1)	0
Diarrhoea	38 (41.8)	3 (3.3)	23 (25.0)	0
Headache	20 (22.0)	1 (1.1)	39 (42.4)	4 (4.3)
Constipation	22 (24.2)	0	31 (33.7)	2 (2.2)
Decreased appetite	28 (30.8)	3 (3.3)	21 (22.8)	1 (1.1)
Pyrexia	21 (23.1)	0	27 (29.3)	0
Cytokine release syndrome	0	0	45 (48.9)	1 (1.1)
Vomiting	23 (25.3)	2 (2.2)	18 (19.6)	1 (1.1)
Hypokalaemia	20 (22.0)	4 (4.4)	19 (20.7)	4 (4.3)
Febrile neutropenia	22 (24.2)	19 (20.9)	14 (15.2)	11 (12.0)
Lymphopenia	10 (11.0)	8 (8.8)	25 (27.2)	23 (25.0)
Dizziness	13 (14.3)	0	20 (21.7)	0
Hypomagnesaemia	19 (20.9)	1 (1.1)	13 (14.1)	0
Insomnia	11 (12.1)	0	19 (20.7)	0
Hypotension	4 (4.4)	0	19 (20.7)	3 (3.3)

(Source: Clinical Safety Overview Table 5.1-1, p.71)

6.1.12.5 Adverse Events of Special Interest (AESI)

Table 13 summarizes the treatment-emergent AESI post study treatment. The frequency of AESIs was greater in the liso-cel arm than in the SOC. The most frequently reported AESI category reported in both arms was neurological toxicity.

Table 13. AESI reported in Study BCM-003

Safety Parameters	No. of Subjects (%)			
	SOC Arm (N = 91)		Liso-cel Arm (N = 92)	
	Any Grade	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Treatment-emergent AESIs	68 (74.7)	25 (27.5)	83 (90.2)	51 (55.4)
Neurological toxicity	58 (63.7)	6 (6.6)	59 (64.1)	12 (13.0)
iiNT	N/A	N/A	11 (12.0)	4 (4.3)
Cytokine release syndrome	0	0	45 (48.9)	1 (1.1)
Prolonged cytopenia	3 (3.3)	3 (3.3)	40 (43.5)	40 (43.5)
Severe infections (Grade ≥ 3)	19 (20.9)	19 (20.9)	14 (15.2)	14 (15.2)
Hypogammaglobulinaemia	2 (2.2)	0	8 (8.7)	1 (1.1)
Infusion-related reaction (IRR)	3 (3.3)	0	6 (6.5)	2 (2.2)
Tumor lysis syndrome (TLS)	2 (2.2)	1 (1.1)	0	0
Macrophage activation syndrome (MAS)	0	0	1 (1.1)	0
Second primary malignancy	0	0	0	0

(Source: Clinical Safety Overview Table 5.1-1, p.72)

6.2 Study # 017006

6.2.1 Objectives

To measure the efficacy and safety of liso-cel in adult subjects with R/R LBCL who are ineligible for HDST and HSCT.

6.2.2 Design Overview

Study 017006 was an open-label, single-arm. multicenter, Phase 2 study to assess the antitumor activity, pharmacokinetics, and safety of liso-cel in subjects that were R/R after first-line immunochemotherapy for LBCL and were deemed by the treating physician to be ineligible for HDCT and HSCT and met at least one protocol-specified transplant non-eligible criterion (See Section 5.1 of the protocol).

The primary analysis was performed after approximately 62 subjects have been treated with liso-cel and followed for at least 6 months after first response (either CR or PR), or until death, PD, or withdrawal from study.

6.2.3 Population

Key elements of eligibility criteria for Study 017006 are listed below.

- Eligible subjects were ≥ 18 years of age with R/R aggressive large B-cell NHL.
- Subjects must be deemed ineligible for auto-HSCT by the investigator.
- The trial excluded subjects with previous treatment with CD19-targeted therapy.
- The trial excluded subjects with central nervous system-only involvement by malignancy.

6.2.4 Study Treatments or Agents Mandated by the Protocol

A single liso-cel dose of 100×10^6 CAR+ T cells.

6.2.6 Sites and Centers

Eighteen (18) study sites in US.

6.2.7 Surveillance/Monitoring

An independent DSMB will review cumulative study data approximately quarterly over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. An IRC will also be established to determine response and progression status.

6.2.8 Endpoints and Criteria for Study Success

In Study 017006, the primary endpoint was ORR, which was defined as the proportion of subjects with a BOR of either CR or PR. In this memo, the IRC-FDA algorithm was used as the primary method to assess response. The response assessed by IRC was used for sensitivity analysis.

The study protocol also included several secondary efficacy endpoints: CR rate, DOR, PFS, EFS and OS.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

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 liso-cel-treated efficacy analysis set.
Note: In order to provide a basis for historical ORR rate to properly size this trial, the applicant performed a meta-analysis[3] (based on fixed and random effects models) on data from 12 published studies of second-line therapy for patients with R/R aggressive LBCL. This meta-analysis showed an ORR of 46% (95% CI: 43%, 50%) using the fixed-effect model and 52% (95% CI: 44%, 59%) using the random-effects model. Thus, the ORR threshold of 50% was chosen. This meta-analysis was performed and then included in the original protocol for Study 017006 (submitted on August 31, 2017) before starting the trial (first patient first visit on July 26, 2018).

Analysis populations:

- *Leukapheresed Analysis Set* included all subjects who signed the informed consent form and underwent leukapheresis.
- *Liso-cel-treated Analysis Set* included all subjects who had received at least one infusion of liso-cel investigational product.
- *Liso-cel-treated Efficacy Analysis Set* included all subjects in the liso-cel-treated Analysis Set who had PET-positive disease present before liso-cel infusion.

Statistical methods:
Primary efficacy analyses were conducted on the liso-cel-treated efficacy analysis set. IRC-FDA assessment of disease status was used.

Primary endpoint
The primary efficacy endpoint, ORR, was calculated along with the 2-sided 95% exact Clopper-Pearson confidence interval. The number and proportion of subjects who were evaluated as CR, PR, SD, PD, or NE were also tabulated.

Secondary endpoints
The analysis of CR rate was conducted similarly to the analysis of ORR. The KM method was used for the analysis of DOR, PFS, EFS and OS. Based on the nature of single-arm study, only DOR analyses would be shown in this memo.

Sample size and power calculation:
A sample size of 62 subjects in the liso-cel-treated efficacy analysis set provided at least 85% power to reject the null hypothesis of ORR $\leq 50\%$ assuming the target ORR of 70% using an exact binomial test with 1-sided significance level 0.025. Assuming a 15% drop-

out rate from leukapheresis prior to liso-cel infusion, it was anticipated that approximately 73 subjects would be leukapheresed in the study.

Sensitivity analyses:
Sensitivity analyses of response and DOR were performed based on:

- The liso-cel-treated efficacy analysis set per IRC assessment
- The leukapheresed analysis set per IRC-FDA algorithm and IRC assessment, respectively

Subgroup analyses:
In the liso-cel-treated efficacy analysis set, subgroup analyses were performed based on age, sex, race and a variety of other baseline clinical characteristics.

Missing data:
All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered as non-responders. For assessment of DOR, loss to follow-up subjects would be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Table 14 summarizes the analysis sets in Study 017006. Leukapheresed analysis set included 74 subjects. Of 74 subjects, 61 (82.4%) subjects received at least one dose of liso-cel treatment that constituted the liso-cel-treated analysis set, and all these 61 subjects were efficacy evaluable that constituted the liso-cel-treated efficacy analysis set.

Table 14. Analysis sets in Study 017006

Analysis Set	N (%)
Screened set	93
Leukapheresed analysis set	74 (100)
Liso-cel-treated analysis set	61 (82.4)
Liso-cel-treated Efficacy analysis set	61 (82.4)

Note: The data cut-off date for Study 017006 is May 28, 2021.
(Source: FDA statistical reviewer's summary)

6.2.10.1.1 Demographics

Table 15 shows the demographic information for subjects in the leukapheresed and liso-cel-treated efficacy analysis set, respectively. Subjects' demographics in these two analysis sets were similar. As in this study, liso-cel-treated analysis set and liso-cel-treated efficacy analysis set are the same, the results only based on liso-cel-treated efficacy analysis set would be shown in the following sections.

Table 15. Subject demographics (leukapheresed, efficacy analysis set) in Study 017006

	Leukapheresed set, n=74	Efficacy analysis set, n=61
Age (years)		
Mean (STD)	72.8 (6.57)	73.1 (6.64)
Median (min, max)	73.5 (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 statistical reviewer's summary)

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 16 shows the baseline characteristics for subjects in the leukapheresed and liso-cel-treated efficacy analysis set, respectively. There were no outstanding differences with respect to subject baseline characteristics between these two analysis sets.

Table 16. Baseline characteristics (leukapheresed, efficacy analysis set) in Study 017006

	Leukapheresed set, n=74	Efficacy analysis set, n=61
ECOG score at screening, n (%)		
0	22 (29.7%)	19 (31.1%)
1	32 (43.2%)	26 (42.6%)
2	20 (27.1%)	16 (26.2%)
sAAIPI at screening, n (%)		
0-1	36 (48.6%)	34 (55.7%)
2-3	37 (50.0%)	26 (42.6%)
Missing	1 (1.4%)	1 (1.6%)
pre-LDC CrCl, n (%)		
< 50 mL/min	7 (9.5%)	6 (9.8%)
50-60 mL/min	9 (12.2%)	8 (13.1%)
⩾ 60 mL/min	50 (63.5%)	47 (77.0%)
Missing	8 (10.8%)	0
Best response to first-line therapy, n (%)		
CR	35 (47.3%)	29 (47.5%)
PR	17 (23.0%)	15 (24.6%)
SD	6 (8.1%)	4 (6.6%)
PD	16 (21.6%)	13 (21.3%)

CrCl = creatinine clearance
(Source: FDA statistical reviewer's summary)

6.2.10.1.3 Subject Disposition

At the time of the data cutoff date May 28, 2021, out of the 61 subjects in the liso-cel-treated analysis set who received the liso-cel, 5 had completed the study, 32 were still ongoing in the study, and 24 had discontinued. Among the 24 subjects who discontinued, the most common reason for discontinuation was death (N = 18).

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Table 17 shows the best response per IRC-FDA algorithm for leukapheresed and liso-cel-treated efficacy analysis set, respectively.

Table 17. BOR per IRC-FDA (leukapheresed, efficacy analysis set) in Study 017006

	Leukapheresed set, n=74	Efficacy analysis set, n=61
ORR (CR+PR), n (%)	49 (66.2%)	48 (78.7%)
95% CI	(54.3%, 76.8%)	(66.3%, 88.1%)
CR rate, n (%)	34 (45.9%)	33 (54.1%)
95% CI	(34.3%, 57.9%)	(40.8%, 66.9%)
PR rate, n (%)	15 (20.3%)	15 (24.6%)
95% CI	(11.8%, 31.2%)	(14.5%, 37.3%)
SD, n (%)	1 (1.4%)	1 (1.6%)
PD, n (%)	11 (14.9%)	11 (18.0%)
NE, n (%)	13 (17.6%)	1 (1.6%)

(Source: FDA statistical reviewer's analysis)

In the liso-cel-treated efficacy analysis set of 61 subjects, 48 subjects (78.7%) 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%. Among the 48 responders, 33 subjects (54.1%) had a best response of CR, and 15 (24.6%) subjects had a best response of PR.

Table 18 shows the best response based on IRC assessment for leukapheresed and liso-cel-treated efficacy analysis set, respectively. Analysis of ORR including CR rate assessed by IRC results in the same conclusion as assessed by IRC-FDA algorithm.

Table 18. BOR per IRC (leukapheresed, efficacy analysis set) in Study 017006

	Leukapheresed set, n=74	Efficacy analysis set, n=61
ORR (CR+PR), n (%)	50 (67.6%)	49 (80.3%)
95% CI	(55.7%, 78.0%)	(68.2%, 89.4%)
CR rate, n (%)	34 (45.9%)	33 (54.1%)
95% CI	(34.3%, 57.9%)	(40.8%, 66.9%)
PR rate, n (%)	16 (21.6%)	16 (26.2%)
95% CI	(12.9%, 32.7%)	(15.8%, 39.1%)
SD, n (%)	3 (4.1%)	3 (4.9%)
PD, n (%)	8 (10.8%)	8 (13.1%)
NE, n (%)	13 (17.6%)	1 (1.6%)

(Source: FDA statistical reviewer's analysis)

To evaluate the concordance in assessment of disease status, BOR assessed by IRC-FDA and IRC assessments for liso-cel-treated efficacy analysis set was shown in Table 19.

Table 19. Concordance between IRC-FDA and IRC assessment in the evaluation of the BOR (efficacy analysis set) in Study 017006

Frequency	IRC assessment					
IRC-FDA	CR	PR	SD	PD	NE	Total
CR	33	0	0	0	0	33
PR	0	15	0	0	0	15
SD	0	0	1	0	0	1
PD	0	1	2	8	0	11
NE	0	0	0	0	1	1
Total	33	16	3	8	1	61

(Source: FDA statistical reviewer's summary)

The assessments based on IRC-FDA and IRC made the same BOR call in 95.1% (=58/61) of the cases. 48 subjects were determined to be responders by both IRC-FDA and IRC (33 CRs, 15 PRs) assessments.

6.2.11.2 Analyses of Secondary Endpoint

DOR

Table 20 summarizes the DOR result in the liso-cel-treated efficacy analysis set per IRC-FDA and IRC assessments, respectively.

Table 20. DOR result per IRC-FDA and IRC (efficacy analysis set) in Study 017006

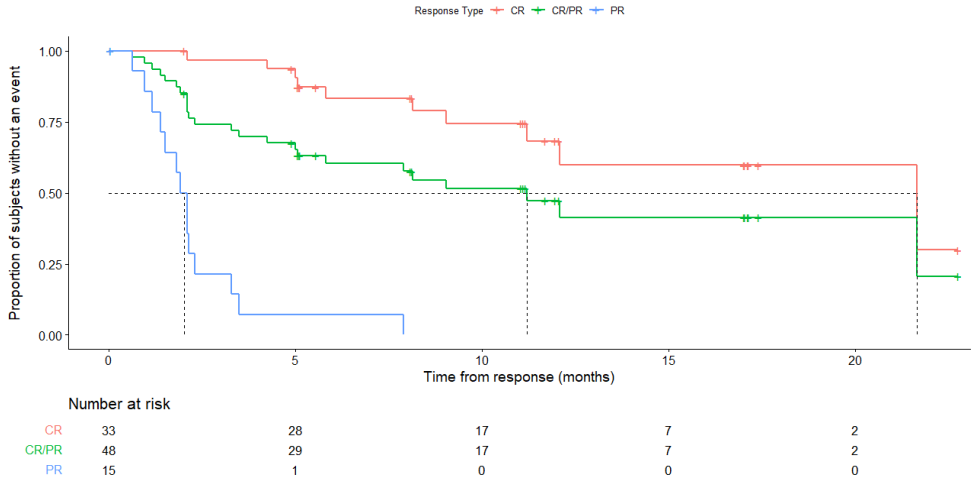
	IRC-FDA algorithm	IRC assessment
Number of subjects achieved CR or PR, n	48	49
Number of events, n (%)	24 (50%)	22 (44.9%)
Progression	23 (47.9%)	21 (42.9%)
Death	1 (2.1%)	1 (2.0%)
Censored, n (%)	24 (50%)	27 (55.1%)
Ongoing	22 (45.8%)	22 (44.9%)
Completed the Study	1 (2.1%)	1 (2.0%)
Discontinued the study	1 (2.1%)	1 (2.0%)
Received a new anticancer therapy	0	3 (6.1%)
DOR (months)		
median	11.20	11.20
95% CI	(4.99, NR)	(5.06, NR)
Follow-up (months)		
median	11.2	11.2
95% CI	(11.0, 17.0)	(8.1, 16.0)
Percentage of subjects with response duration (%)		
≥6 months (95% CI)	60.4 (44.6, 73.0)	61.9 (45.9, 74.4)
≥12 months (95% CI)	47.3 (30.6, 62.3)	48.5 (31.4, 63.6)
≥24 months (95% CI)	20.7 (1.9, 53.4)	42.4 (24.3, 59.4)

(Source: FDA statistical reviewer's analysis)

For analysis of DOR per IRC-FDA algorithm, the overall median was 11.20 months with a lower 95% limit of 4.99 months and an unattainable upper limit. The DOR result was similar per IRC assessment.

Figure 10 shows KM curve of DOR per IRC-FDA algorithm by response type (CR or PR). Complete responders had substantially longer DOR than the partial responders. The median DOR for the partial responders was 2.0 months (95% CI: 1.15, 2.3) and the median DOR was 21.7 months for complete responders (95% CI: 11.2, NR).

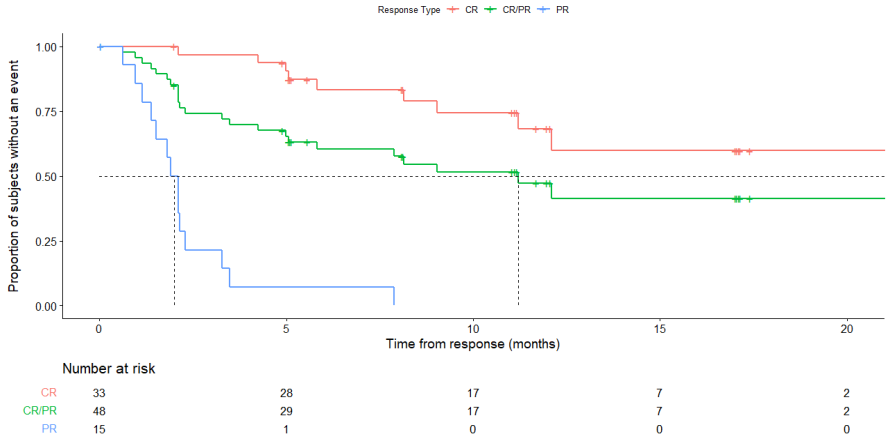
Figure 10. KM curve of DOR per IRC-FDA algorithm by response type in Study 017006



(Source: FDA statistical reviewer's analysis)

Figure 11 shows KM curve of DOR per IRC assessment by response type (CR or PR). Similar to the result of DOR assessed by IRC-FDA algorithm, complete responders had substantially longer DOR than the partial responders. The median DOR for the partial responders was 2.1 months (95% CI: 1.38, 2.3) and the median DOR was not reached for complete responders (95% CI: 11.2, NR).

Figure 11. KM curve of DOR per IRC assessment by response type in Study 017006

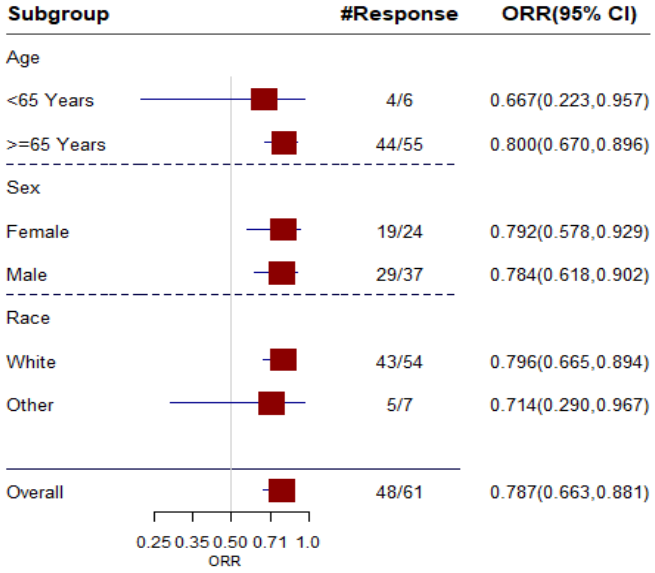


(Source: FDA statistical reviewer's analysis)

6.2.11.3 Subpopulation Analyses

Figure 12 shows the forest plot of ORR in the liso-cel-treated efficacy analysis set by age group, sex and race. 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 almost each subgroup, except the subgroup with Age < 65 Years and the subgroup with Other Race. However, the number of subjects in these two subgroups were too small to make any conclusion.

Figure 12. Forest plot of ORR by subgroups in Study 017006



(Source: FDA statistical reviewer's analysis)

6.2.12 Safety Analyses

This section briefly summarizes safety results of Study 017006.

6.2.12.1 Methods

Descriptive statistic was used to summarize safety data for Study 017006. The safety analysis set in this section included a total of 61 subjects who received at least one dose of liso-cel treatment.

6.2.12.3 Deaths

Among 61 treated subjects, 18 (29.5%) subjects died. The most frequently reported reason for deaths was disease progression (N=14), followed by adverse events (N=3) and kidney issue (N=1).

6.2.12.4 Nonfatal Serious Adverse Events

Table 22 summarizes the treatment-emergent non-fatal SAEs reported in at least 2% of treated subjects in any grade in Study 017006. A total of 20 subjects experienced at least one treatment-emergent SAEs. The most frequently reported treatment-emergent SAE was immune system disorders.

Table 22. Treatment-emergent non-fatal SAEs reported in >= 2% of treated subjects in Study 017006

System Organ Class Preferred Term[a]	N = 61 n (%)
Subjects with any serious TEAEs	20 (32.8)
Immune system disorders	**8 (13.1)**
Cytokine release syndrome	8 (13.1)
Gastrointestinal disorders	**3 (4.9)**
Upper gastrointestinal hemorrhage	2 (3.3)
Lower gastrointestinal hemorrhage	1 (1.6)
Obstruction gastric	1 (1.6)
Infections and infestations	**3 (4.9)**
Bacteremia	1 (1.6)
COVID-19	1 (1.6)
COVID-19 pneumonia	1 (1.6)
Staphylococcal infection	1 (1.6)
Stenotrophomonas sepsis	1 (1.6)
Musculoskeletal and connective tissue disorders	**3 (4.9)**
Muscular weakness	2 (3.3)
Arthralgia	1 (1.6)
Neck pain	1 (1.6)
Psychiatric disorders	**3 (4.9)**
Confusional state	3 (4.9)
Disorientation	1 (1.6)
Injury, poisoning and procedural complications	**2 (3.3)**
Fall	1 (1.6)
Hip fracture	1 (1.6)
Investigations	**2 (3.3)**
Blood bilirubin increased	1 (1.6)
Weight decreased	1 (1.6)
Respiratory, thoracic and mediastinal disorders	**2 (3.3)**
Pulmonary embolism	2 (3.3)

(Source: Interim Clinical Study Report for Study 017006 Table 9.3.2-1, p.156)

6.2.12.5 AESI

Table 23 summarizes the treatment-emergent AESI post study treatment in Study 017006. The most frequently reported AESI category reported was cytokine release syndrome (CRS, 23 [37.7%] subjects).

Table 23. AESI reported in >= 2% of treated subjects in Study 017006

AESI	N=61, n (%)
CRS or investigator-identified neurotoxicity (iiNT)	30 (49.2)
CRS	23 (37.7)
iiNT	19 (31.1)
Grade ≥ 3 Infections	4 (6.6)

(Source: Interim Clinical Study Report for Study 017006 abbreviated table 9.4-1, p.159)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support the efficacy and safety of the proposed product comes from two studies: Study BCM-003 and 017006. Study BCM-003 was a

randomized, open-label, multicenter study in adult subjects that were R/R after first-line therapy for LBCL and were eligible for HDCT and autologous HSCT. In Study BCM-003, 184 patients were randomized in a 1:1 ratio to receive liso-cel or SOC therapy. The randomization was stratified by response to first-line therapy (refractory versus relapsed), and sAAIPI (0 to 1 versus 2 to 3). The primary endpoint was EFS determined by IRC-FDA algorithm. Study 017006 was a single-arm, open-label, multicenter study in adult subjects that were R/R after first-line immunochemotherapy for LBCL and were ineligible for HDCT and HSCT. In Study 017006, 61 subjects were received liso-cel and the primary endpoint was ORR assessed by IRC-FDA algorithm.

For Study BCM-003, subjects randomized to receive liso-cel had statistically significant improvement in EFS compared with subjects randomized to receive SOC. The median EFS was 9.5 months (95% CI: 5.8, NR) for the liso-cel arm and 2.4 months (95% CI: 2.2, 4.6) for the SOC, with a stratified hazard ratio of 0.404 (95% CI: 0.267, 0.612) in favor of liso-cel, and a p-value<0.0001 based on a stratified Cox-PH model. Subjects in the liso-cel arm had statistically significantly higher CR rate compared with subjects in the SOC, and also had statistically significant improvement in PFS compared with subjects randomized to receive SOC. For Study 017006, the ORR as assessed by the IRC-FDA algorithm was 78.7% (48/61; 95% CI: 66.3%, 88.1%) and the lower limit of the 95% exact Clopper-Pearson confidence interval was 66.3% which was above the pre-specified null hypothesis rate of 50%. The median DOR was 11.2 months (95% CI: 5.8, NR) for all responders. The median DOR for the partial responders was 2.0 months (95% CI: 1.5, 3.5) and for complete responders, was 21.7 month (95% CI: 12.1, NR).

10.2 Conclusions and Recommendations

Both Study BCM-003 and 017006 met the pre-specified efficacy criteria. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication for BREYANZI in this BLA efficacy supplement.

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3. BMS-986387: Comparative Effectiveness of Lisocabtagene Maraleucel (Liso-Cel) As Second-Line Therapy in Patients With Transplant Non-Eligible Relapsed/Refractory Large B-Cell Lymphoma in Clinical Studies Versus Conventional Treatment in Real-World Historical Controls; Bristol Myers Squibb Company (Study CA082-014); 2021.

APPENDIX

Situation	**Date of Subject has event or is Censored**	**Situation Outcome**
No baseline, or no post-baseline response assessment and no death	Randomization date	Censor
Death	Death date	Event
Progressive disease	Progressive disease date	Event
Failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion)	9 weeks post-randomization assessment date (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion)	Event
Start of a new antineoplastic therapy due to efficacy concerns	Date of imaging (or other objective finding) that serves as the basis of starting a new antineoplastic therapy*	Event
Start of a new antineoplastic therapy for reasons other than efficacy concerns	Last adequate response assessment date	Censor
Failure to proceed to HDCT and HSCT due to refusal or failure to collect or mobilize stem cells	Last adequate response assessment date	Censor
No death, no progressive disease, no failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of SOC for Arm A and 5 weeks after the JCAR017 infusion) and no start of new antineoplastic therapy due to efficacy concerns	Last adequate response assessment date	Censor

* the event date should be interpreted as the latest disease assessment available before start of a new antineoplastic therapy due to efficacy concerns, either based on IRC or investigator's assessment

(Source: Study BCM-003 SAP version 1.2 Table 15, p.52)