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Application Type	PAS Efficacy BLA
STN	125643/394
CBER Received Date	September 30, 2021
PDUFA Goal Date	April 1, 2022
Division / Office	DB/OBE
Committee Chair	Poornima Sharma
Clinical Reviewer(s)	Poornima Sharma
Project Manager	Crystal Melendez
Priority Review	Yes
Reviewer Name(s)	Xue Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Lead, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
Applicant	Kite Pharma
Established Name	axicabtagene ciloleucel
Trade Name	YESCARTA
Pharmacologic Class	CD19-directed genetically-modified autologous T cell
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	The target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.
Proposed Indication(s) and Intended Population(s)	Adult patients with relapsed or refractory large B-cell lymphoma

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GLOSSARY

ASCT	autologous stem cell transplant
BLA	Biologics Licensure Application
BOR	best overall response
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CRS	cytokine release syndrome
CSR	clinical study report
DLBCL	diffuse large B cell lymphoma
DOR	duration of remission
Data Safety Monitoring Board	DSMB
EFS	event free survival
FAS	full analysis set
HDT	high-dose therapy
HGBL	high-grade B-cell lymphoma
IPI	International Prognostic Index
IRC	independent review committee
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
LBCL	large B-cell lymphoma
ORR	overall remission rate
OS	overall survival
PAS	Prior Approval Supplement
PD	progressive disease
PFS	Progression-free survival
PR	partial response
QoL	quality of life
r/r	relapsed/refractory
SAE	serious adverse event
SCT	stem-cell transplantation
SD	stable disease
SOC	standard of care
TBI	total body irradiation
NHL	non-Hodgkin lymphoma

1. EXECUTIVE SUMMARY

Axicabtagene ciloleuel is an engineered autologous T cell immunotherapy. Axicabtagene ciloleuel received the FDA Biological Licensure Approval (BLA) approval in October 2017 for the indication of "Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy". In this Prior Approval Supplement (PAS), the applicant seeks labeling change to remove "after two or more lines of systemic therapy" from the indication and the new proposed indication is "Adult patients with relapsed or refractory large B-cell lymphoma".

The primary source of evidence to support the efficacy and the safety of the proposed product comes from study ZUMA-7, which was a randomized, open-label, multicenter trial in adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after first-line rituximab and anthracycline-based chemotherapy. In ZUMA-7, 359 patients were randomized in a 1:1 ratio to receive axicabtagene ciloleuel or Standard of Care (SOC) therapy. The primary endpoint was event-free survival (EFS) determined by blinded central review.

Based on 252 EFS events, subjects randomized to receive axicabtagene ciloleucel had statistically significant improvement in EFS compared with subjects randomized to receive SOC. The median EFS was 8.3 months (95% CI: 4.5 to 15.8) for the axicabtagene ciloleucel arm and 2.0 months (95% CI: 1.6 to 2.8) for the SOC arm, with a stratified hazard ratio of 0.398 (95% CI: 0.308 to 0.514) in favor of axicabtagene ciloleucel, and a stratified log-rank test p-value<0.0001. Subjects in the axicabtagene ciloleucel arm had statistically significantly higher objective response rate (ORR) compared with subjects in the SOC arm. The ORR was 83% (95% CI: 77.1%, 88.5%) for the axicabtagene ciloleucel arm and 50% (95% CI: 42.7%, 57.8%) for the SOC arm, with a difference in ORR of 33.1% (95% CI: 23.2, 42.1), and p-value < 0.0001 based on the Cochran-Mantel-Haenszel (CMH) test. The compete response (CR) rate in the axicabtagene ciloleucel arm and the SOCT arms were 65% (95% CI: 57.6%, 71.9%) and 32% (95% CI: 25.6%, 39.8%), respectively. A planned interim analysis on OS was conducted at the time of the final EFS analysis. With 157 death occurred, which was 75% information fraction, the OS outcome did not cross the interim stopping boundary for early efficacy claim. The interpretation of the OS results at the interim look was complicated by the cross-over events: 100 subjects (56%) in SOC arm later received axicabtagene ciloleucel as new lymphoma therapy.

Study ZUMA-7 met its primary efficacy endpoint: the pre-specified null hypothesis on EFS was rejected, and the key secondary endpoint of ORR was also met. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication for axicabtagene ciloleucel in this BLA Prior Approval Supplement.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Based on information submitted by the applicant, Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes and, to a lesser extent, in T lymphocytes and natural killer cells. NHL is the most prevalent hematological malignancy and is the seventh most common new cancer in the United States (US), accounting for 4% of all new cancer cases and 3% of cancer-related deaths. The most common subtype of NHL is diffuse large B-cell lymphoma (DLBCL), an aggressive subtype accounting for approximately 30% to 40% of all NHL cases and > 80% of all cases of LBCL.

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

According to the applicant, the current standard of care for the first-line treatment of DLBCL is the chemotherapeutic regimen cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP, rituximab-based chemoimmunotherapy). Patients with LBCL, including DLBCL, NOS, and HGBL, who are refractory to or relapse after first-line therapy, have poor prognosis. In the LNH-98.5 trial, approximately 40% of patients relapse after R-CHOP, and 70% of these patients die within the first two years after progression despite salvage therapy, with a median OS of 0.7 years after progression.

According to the applicant, standard second-line therapy in the curative setting for LBCL is comprised of platinum-containing salvage chemoimmunotherapy followed by high-dose therapy (HDT) and autologous stem cell transplant (auto-SCT) if the patient responds to salvage chemotherapy. While HDT-auto-SCT has curative potential, only half of patients respond to second-line salvage chemotherapy and are able to proceed to auto-SCT. Furthermore, disease progression can occur at any point preparing for or after auto-SCT, increasing the risk of death due to early transplant-related mortality. Poor outcomes are observed for patients who cannot undergo auto-SCT. Thus, treatment of patients with relapsed/refractory (r/r) LBCL remains challenging and there is a high unmet need for better curative therapies.

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

Table 1 summarizes the major pre-submission regulatory activities associated with this sBLA.

Table 1. Major pre-submission regulatory activities

Meeting Topic (Type); Discussion Points	Format	Meeting Date
SPA Meeting (Type A) Discussion of the ZUMA-7 protocol for SPA	Teleconference	08 September 2017
Format and Content Meeting (Type B) Discussion of the format and content of the planned sBLA for r/r LBCL	Teleconference	21 August 2020
EFS Event Rate Meeting (Type B) Analysis of the decline of EFS event rate in ZUMA-7 and discussion about amending the protocol to lower the event count needed to trigger the primary analysis	Teleconference	09 February 2021
Pre-sBLA Topline Meeting (Type B) Discussion of topline data	Teleconference	07 September 2021

(Source: original Table 3 Section 1.6 clinical overview sBLA 125643/394)

Table 2 summarizes the major post-submission regulatory activities associated with this sBLA.

Table 2. Major post-submission regulatory activities

Milestone	Date
DCC Receipt Date	September 30, 2021
Filling Letter issued	November 29, 2021
Mid-Cycle Meeting	January 4, 2022
PUDUFA Action Due Date	April 1, 2022

(Source: FDA statistical reviewer)

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 ZUMA-7, which is 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 is clinical study reports (CSR) and data sets submitted in module 5 of the BLA submission.

5.3 Table of Studies/Clinical Trials

Table 3 summarizes the studies included in the sBLA submission.

Table 3. Studies supporting the proposed indication in the sBLA submission

Type of Study	Description of Study	Role in the Application
AXICABTAGENE CILOLEUCEL-107 (ZUMA-7)	Phase 3, multicenter, randomized, open- label study evaluating the safety and efficacy of axicabtagene ciloleucel compared with SOCT in adult subjects with r/r LBCL	Efficacy and primary safety
AXICABTAGENE CILOLEUCEL-101 (ZUMA-1)	Phase 1/2 (Cohorts 1 and 2) multicenter study of the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL	Supporting safety

(Source: Abbreviated Table 2 Section 1.2 clinical overview sBLA 125643/394)

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 (Study ZUMA-7)

6.1.1 Objectives

Primary Objective:

- To evaluate if axicabtagene ciloleucel is superior to SOC as measured by event free survival (EFS) as determined by blinded central review

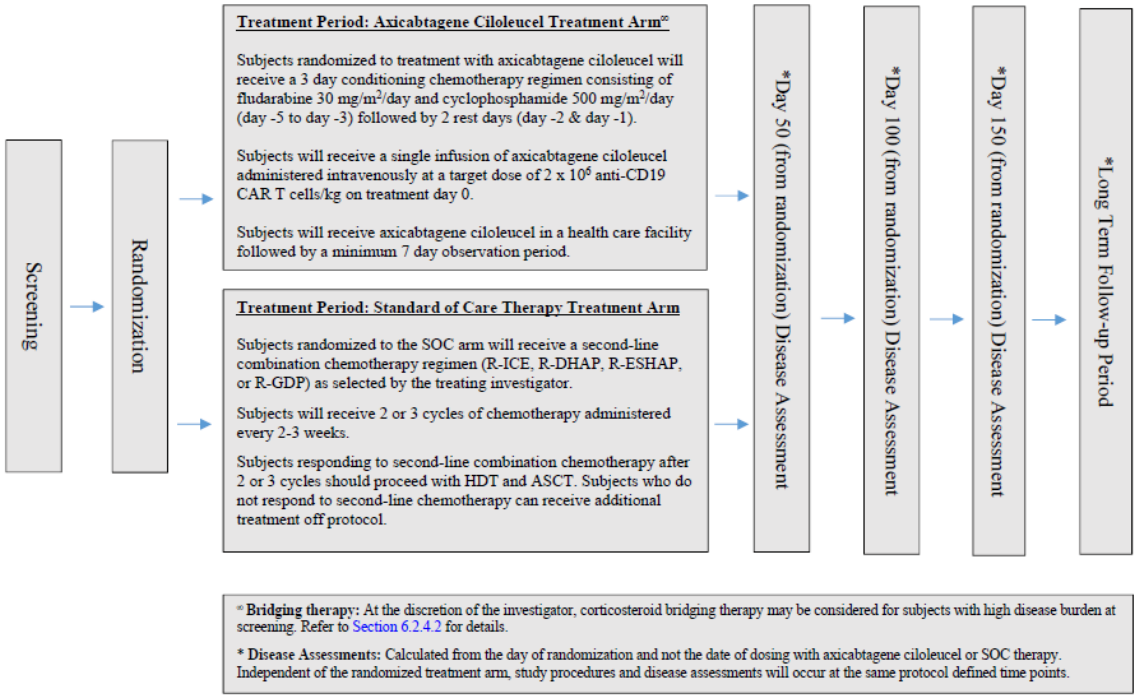
Secondary Objectives:

- To evaluate the effect of axicabtagene ciloleucel compared to SOC on objective response rate (ORR) as determined by blinded central review
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on overall survival (OS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on progression free survival (PFS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on duration of response (DOR) and duration of complete response among responding subjects as determined by blinded central review
- To evaluate the safety of axicabtagene ciloleucel compared to SOC
- To evaluate the effect of axicabtagene ciloleucel on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC

6.1.2 Design Overview

Figure 1 shows the study schema of ZUMA-7. Adult subjects with r/r LBCL after first-line rituximab and anthracycline-based chemotherapy were randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOC. Randomization was stratified by response to first line therapy (primary refractory, vs relapse ≤6 months of initiating first line therapy vs relapse > 6 and ≤ 12 months of initiating first line therapy) and second line age-adjusted IPI (0-1 vs. 2-3) as assessed at the time of screening.
For subjects in the axicabtagene ciloleucel arm, treatment consisted of lymphodepleting chemotherapy followed by a single intravenous infusion of axicabtagene ciloleucel. Bridging therapy of corticosteroids was allowed prior to lymphodepleting chemotherapy for subjects with high disease burden, at the discretion of the investigator. For subjects in the SOC arm, treatment consisted of a single protocol-defined, platinum-based salvage chemotherapy regimen as selected by the treating investigator. Subjects who responded to salvage chemotherapy were to proceed to high-dose therapy (HDT) with or without total body irradiation (TBI), followed by autologous stem cell transplant (auto-SCT).

Figure 1. Study Schema



(Source: original figure 2 Section 7.1 CSR sBLA 125643/394)

6.1.3 Population

The study enrolled adult subjects with r/r LBCL. Detailed inclusion and exclusion criteria are in Section 5 of the study protocol.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For subjects randomized to the control arm of the study, SOC would consist of a protocol-defined, platinum-based salvage combination chemotherapy regimen. Subjects who respond to second-line chemotherapy should proceed to HDT and ASCT.
For subjects randomized to the axicabtagene ciloleucel arm of the study, bridging therapy may be considered for subjects with high disease burden at screening, at the discretion of the investigator. The subjects would receive a 3- day conditioning chemotherapy regimen on day -5 to day -3 followed by two rest days (day -2 and day -1), and a single infusion of axicabtagene ciloleucel administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg on day 0.

6.1.6 Sites and Centers

This study was to be conducted at 60 study centers in North America, Europe, and Israel.

6.1.7 Surveillance/Monitoring
An independent Data Safety Monitoring Board (DSMB) were to meet every 6 months after the first subject is randomized to review safety data and would review safety and efficacy data at the time of the planned interim futility analysis. The DSMB were to be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Event Free Survival (EFS)
Defined as the time from randomization to the earliest of disease progression or relapse, best response of stable disease up to and including the Day 150 assessment, commencement of new lymphoma therapy, and death from any cause

Key secondary endpoints:
- Objective response rate (ORR): defined as the incidence of either a complete response or a partial response by the Lugano Classification as determined by blinded central review
- Overall survival (OS): defined as the time from randomization to death from any cause

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypotheses:
Primary hypothesis: axicabtagene ciloleucel will prolong EFS compared to SOC therapy in adult subjects with relapsed/refractory LBCL.
Key secondary hypothesis:

- axicabtagene ciloleucel will increase ORR compared to SOC therapy in adult subjects with relapsed/refractory LBCL.
- axicabtagene ciloleucel will prolong OS compared to SOC therapy in adult subjects with relapsed/refractory LBCL.

To preserve the overall significance level, statistical testing of the primary and key secondary hypotheses would follow a hierarchical order. EFS would be tested first at the primary EFS analysis. Conditional on a statistically significant improvement in EFS, ORR would be tested at the 2.5% level at the time of the primary EFS analysis. Conditional on a statistically significant improvement in EFS and ORR, OS would be tested up to 2 times at an overall alpha level of 2.5%

Analysis populations

a. Full Analysis Set: all randomized subjects
b. Safety analysis set: all subjects treated with any dose of axicabtagene ciloleucel as protocol therapy or SOC chemotherapy as protocol therapy

Statistical methods

Primary endpoint

A stratified (by randomization stratification factors) log-rank test was used for the primary comparison of EFS.

Additionally, stratified (by randomization stratification factors) Cox regression model was used to provide the estimated EFS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOC.

Kaplan-Meier (KM) curves were presented, and KM estimates and 2-sided 95% confidence intervals were calculated.

Key secondary endpoints

a. ORR

An exact binomial 2-sided 95% confidence interval was generated for the estimated ORR and best response rates for each treatment arm. Wilson's score method with continuity correction was used to calculate 95% confidence intervals for the difference in ORRs between treatment arms.

Conditional upon demonstrating a statistically significant improvement in EFS, testing the significance of ORR was performed with a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratification factors for the common odds ratio of response.

b. OS

The same analyses methods applied to EFS were applied to the analysis of OS.

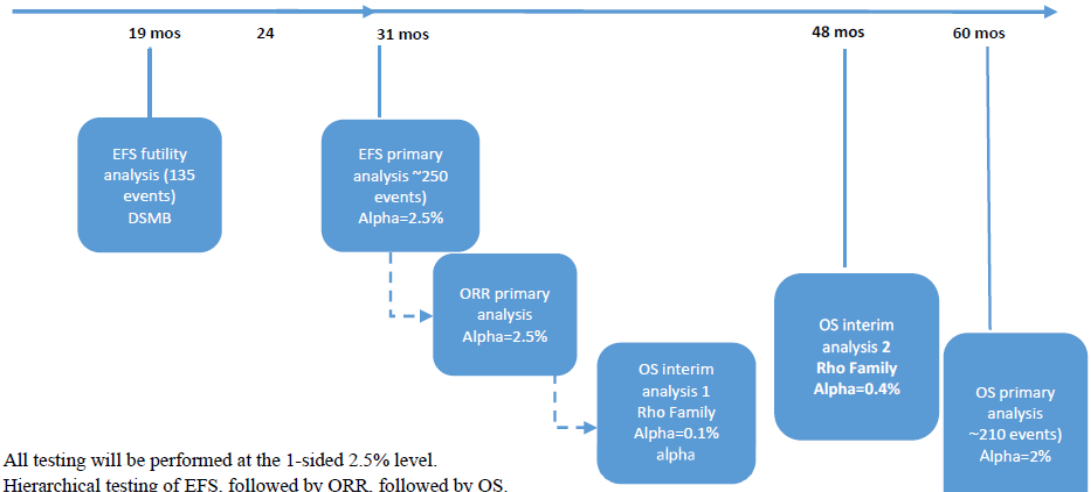
Sample size

The study planned to enroll approximately 350 subjects. The primary analysis was planned when approximately 250 EFS events were observed; the study was sized to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in median EFS (4 months versus 6 months, HR=0.67).

Interim analyses

One interim analysis of EFS and two interim analyses of OS were planned. The interim EFS analysis was for futility and would occur when 135 EFS events had been observed. The futility stopping rule was non-binding. Conditional upon statistically significant tests of EFS and ORR at the primary EFS analysis, testing of OS would be performed. A first interim analysis of OS would occur at the time of the primary EFS analysis and a second interim analysis when approximately 160 deaths occurred or no later than 5 years after the first subject is randomized. A spending function of the Rho family with parameter (rho = 6) would be used to allocate the alpha between the interim analyses of OS and the primary analysis of OS with 0.1% and 0.4% of alpha spent at the first and second interim OS analyses, respectively, and 2% of alpha at the primary analysis of OS. Approximately 110 and 160 OS events were anticipated at the time of the first and second interim OS analyses, respectively (Figure 2).

Figure 2. Interim analyses schema



All testing will be performed at the 1-sided 2.5% level.
Hierarchical testing of EFS, followed by ORR, followed by OS.
Three analyses of OS are planned; a first interim analysis at the time of the primary EFS analysis, a second interim analysis when approximately 160 deaths have been observed or no later than 5 years after the first subject is randomized, and a primary OS analysis when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized.
EFS analyses are event-driven and will occur when the required number of events have been observed regardless of

(Source: original figure 2 Section 10.3 protocol amendment #5 sBLA 125643/394)

Subgroup analysis

Subgroup analyses were planned based on age, sex, race, ethnicity 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

6.1.10.1.1 Demographics

Demographics of subjects enrolled in ZUMA-7 are summarized in Table 4. The median age was 59 years (range: 21 to 81 years), 66% were male, 83% were white, 6% were Asian and 5% were African American. Most subjects (75%) received treatment in North America, 250 (70%) were treated in the United States. Demographics were balanced between the two treatment arms, except for sex, SOC had more male subjects than the axicabtagene ciloleucel did (71% vs. 61%).

Table 4. Subject Demographics (Full Analysis Set)

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N=179)**	**Overall (N = 359)**
Age (years)			
n	180	179	359
Mean (STDEV)	57.1 (12.0)	57.4 (12.2)	57.2 (12.1)

Median (Q1, Q3)	58.0 (52.0, 66.0)	60.0 (49.0, 67.0)	59.0 (51.0, 67.0)
Min, Max	21, 80	26, 81	21, 81
Age category, n (%)			
< 65 years	129 (72)	121 (68)	250 (70)
≥ 65 years	51 (28)	58 (32)	109 (30)
Sex, n (%)			
Male	110 (61)	127 (71)	237 (66)
Female	70 (39)	52 (29)	122 (34)
Ethnicity, n (%)			
Hispanic or Latino	10 (6)	8 (4)	18 (5)
Not Hispanic or Latino	167 (93)	169 (94)	336 (94)
Not Reported	3 (2)	2 (1)	5 (1)
Race, n (%)			
American Indian or Alaska Native	0 (0)	1 (1)	1 (0)
Asian	12 (7)	10 (6)	22 (6)
Black or African American	11 (6)	7 (4)	18 (5)
Native Hawaiian or Other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Region, n (%)			
North America	140 (78)	130 (73)	270 (75)
Europe	34 (19)	45 (25)	79 (22)
Israel	4 (2)	2 (1)	6 (2)
Australia	2 (1)	2 (1)	4 (1)

(Source: original Table 10 CSR report body sBLA 125643/394)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline disease characteristics of subjects enrolled in ZUMA-7 are summarized in Table 5. In total, 74% of patients had primary refractory LBCL, 55% of patients had second-line age-adjusted International Prognostic Index total score of between 0 and 1, 63% had DLBCL, NOS, 19% had HGBL with or without MYC and BCL2 and/or BCL6 rearrangement. Baseline disease characteristics were balanced between the two treatment arms.

Table 5. Subject Baseline Characteristics (Full Analysis Set)

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N = 179)**	**Overall (N = 359)**
ECOG performance status, n (%)			
0	95 (53)	100 (56)	195 (54)

1	85 (47)	79 (44)	164 (46)
Best response to first-line therapy, n (%)			
Complete response	46 (26)	47 (26)	93 (26)
Partial response	60 (33)	62 (35)	122 (34)
Stable disease	11 (6)	11 (6)	22 (6)
Progressive disease	63 (35)	59 (33)	122 (34)
Response to first-line therapy, n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤ 6 months of first-line therapy	9 (5)	9 (5)	18 (5)
Relapse > 6 and ≤ 12 months of first-line therapy	38 (21)	39 (22)	77 (21)
Second-line age-adjusted International Prognostic Index total score, n (%)			
0 - 1	98 (54)	100 (56)	198 (55)
2 - 3	82 (46)	79 (44)	161 (45)
Disease type, n (%)			
DLBCL, NOS	110 (61)	116 (65)	226 (63)
T cell/histiocyte rich LBCL	5 (3)	6 (3)	11 (3)
Epstein-Barr virus (EBV) + DLBCL	2 (1)	0 (0)	2 (1)
Large cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)
HGBL with or without MYC and BCL2 and/or BCL6	43 (24)	27 (15)	70 (19)
Primary cutaneous DLBCL (leg type)	1 (1)	0 (0)	1 (0)
Other	0 (0)	3 (2)	3 (1)

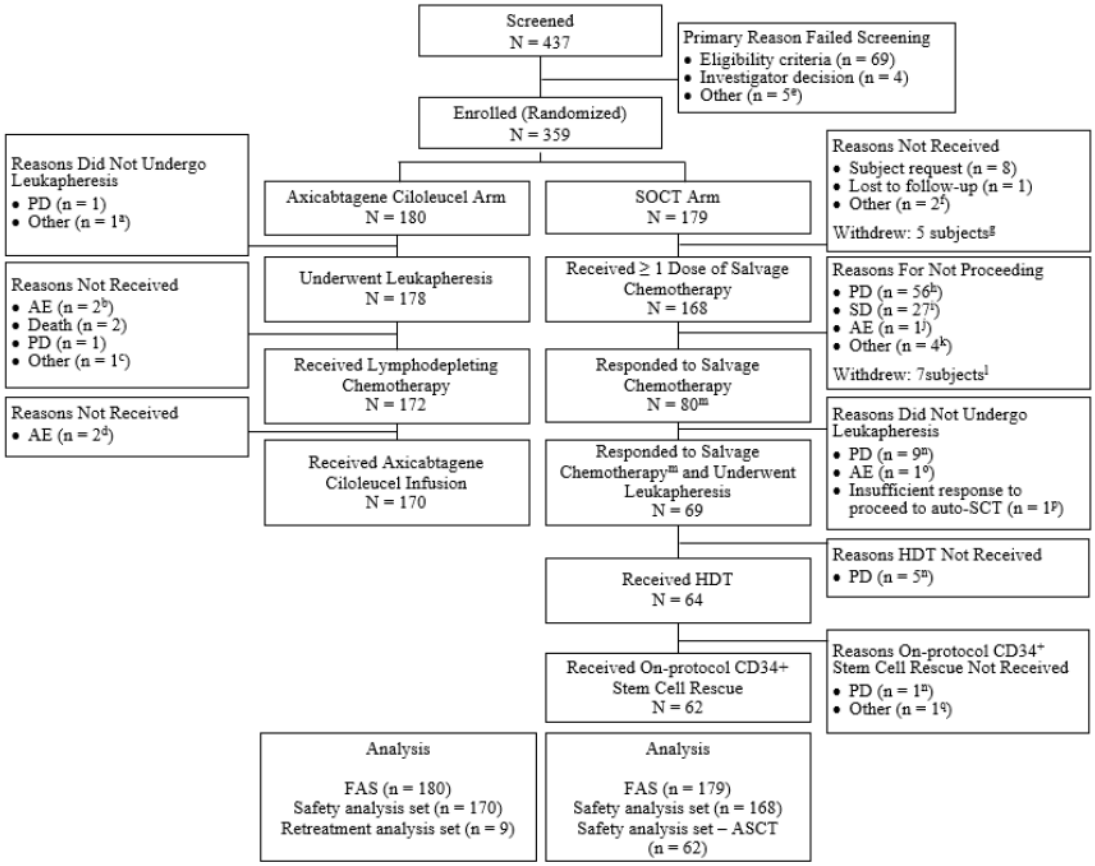
(source: abbreviated Table 11 CSR report body sBLA 125643/394)

6.1.10.1.3 Subject Disposition

Figure 3 shows the subject disposition for ZUMA-7. Of the 180 patients randomized to receive axicabtagene ciloleucel, 178 underwent leukapheresis, and 170 were treated with axicabtagene ciloleucel. Eight patients (4%) were not treated following leukapheresis, primarily due to progressive disease, serious adverse events, or death.

Of the 179 patients randomized to receive standard therapy, 168 patients received any chemotherapy, 62 patients (35%) received HDT and ASCT. The most common reason for not proceeding with ASCT was lack of response to salvage chemotherapy.

Figure 3. Subject disposition



(Source: original Figure 3 report body, CSR, sBLA 125643/394)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Based on 252 EFS events, with a minimum potential follow-up (from last subject randomized to data cutoff date) of 17.5-month, subjects randomized to receive axicabtagene ciloleucel had statistically significant improvement in EFS compared with subjects randomized to receive SOC. The median EFS was 8.3 months (95% CI: 4.5 to 15.8) for the axicabtagene ciloleucel arm and 2.0 months (95% CI: 1.6 to 2.8) for the SOC arm, with a stratified hazard ratio of 0.398 (95% CI: 0.308 to 0.514) in favor of axicabtagene ciloleucel, and a stratified log-rank test p-value<0.0001. The percentage of patients event-free at 12 months was 47.2% (95% CI: 39.8, 54.3) and 17.6% (95% CI: 12.3, 23.6), respectively (Table 6, Figure 4).

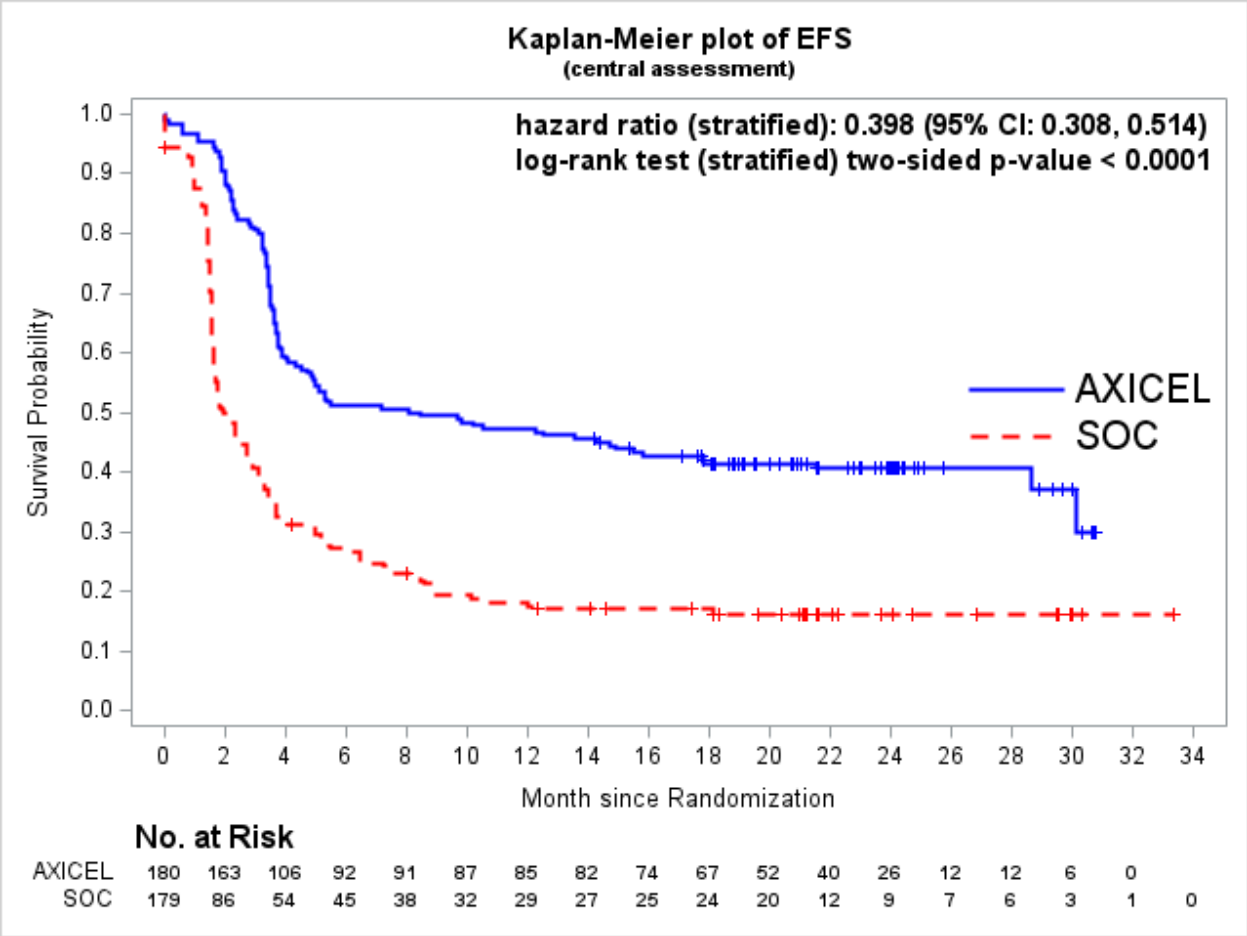
Table 6. Event-free Survival (EFS) per Central Assessment

	Axicabtagene Ciloleucel	**SOC**
Number of subjects	180	179
Events, n (%)	108 (60)	144 (80)
Censored, n (%)	72 (40)	35 (20)
stratified log-rank test, two-sided p-value	<.0001	

Hazard ratio (95% CI), stratified	0.398 (0.308, 0.514)	
KM median (95% CI) EFS time (months)	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
Events		
Disease progression, n (%)	82 (46)	75 (42)
Best response of SD up to and including Day 150 assessment post randomization, n (%)	4 (2)	0 (0)
New lymphoma therapy, n (%)	9 (5)	63 (35)
Axicabtagene ciloleucel retreatment, n (%)	2 (1)	0 (0)
Death from any cause, n (%)	11 (6)	6 (3)
Censoring reason		
Response ongoing, n (%)	72 (40)	28 (16)
Response assessed but no disease at baseline and post-baseline, n (%)	0 (0)	3 (2)
No post-baseline disease assessment, n (%)	0 (0)	1 (1)
Full withdrawal of consent, n (%)	0 (0)	1 (1)
Lost to follow up, n (%)	0 (0)	2 (1)
Event-free rate, % (95% CI)		
3 month	80.6 (74.0, 85.6)	40.5 (33.2, 47.8)
6 month	51.1 (43.6, 58.1)	26.6 (20.2, 33.3)
9 month	49.4 (42.0, 56.5)	19.4 (13.8, 25.6)
12 month	47.2 (39.8, 54.3)	17.6 (12.3, 23.6)

(Source: FDA statistical reviewer)

Figure 4. Kaplan-Meier plot of EFS (Central Assessment)



(Source: FDA statistical reviewer)

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.

Reviewer's comment #1:
Table 6 shows the SOC arm had strikingly higher rate of new lymphoma therapy type of EFS event than the axicabtagene ciloleucel arm. Treating investigators administered new lymphoma therapies, and for an open label trial, this decision may potentially subject to bias: investigators in the SOC arm may tend to administrate new lymphoma therapy more readily than the axicabtagene ciloleucel arm. An EFS endpoint in an open label trial created such a potential issue, a double-blind trial, however, is not an option for an autologous CAR T treatment because the treatment involves bridging therapy and lymphodepleting chemo which are difficult to carry out in a blinded trial, and the treating investigator also needs to closely monitor and manage CRS and other toxicities cause by CAR T.

To evaluate the robustness of the EFS outcomes, we carried out a sensitivity analysis in which events driven by new lymphoma therapy in the SOC arm was carefully examined and 35 such cases was no longer events in this sensitivity analysis.

Twenty-four subjects who responded to SOC chemotherapy (PR or CR) and subsequently received new lymphoma therapy in the absence of disease progression were treated as on-going responder and censored at data cutoff. Five subjects who had SD after only one cycle of chemotherapy, as supposed to at least 2 cycles per protocol, and subsequently received new lymphoma therapy in the absence of disease progression were also treated as on-going responder and censored at data cutoff in the sensitivity analysis. In addition, five subjects who had new lymphoma therapy but otherwise did not receive any protocol specified therapy were censored, instead of being an event, at randomization. The outcome of this sensitivity analysis was consistent with that of the primary analysis in that the EFS was significantly longer with axicabtagene ciloleucel than with SOC, with the stratified log-rank test two-sided p-value =0.0087, the stratified hazard ratio 0.7 (95% CI: 0.535, 0.916). The outcome of this highly conservative sensitivity analysis shows the robustness of the EFS results.

Though the EFS endpoint in an open label trial has its limitation, efficacy of axicabtagene ciloleucel was not solely evaluated on this endpoint. Efficacy was further evaluated in the secondary endpoints such as ORR, PFS, OS, and DOR as described in Section 6.1.11.2. Different from EFS, for the PFS endpoint new lymphoma was not an event but instead triggered censoring. In addition, the OS endpoint did not distinguish new lymphoma therapy from protocol specified therapy. The impact of potential bias in new lymphoma therapy administration was minimized in the assessment of these two endpoints.

6.1.11.2 Analyses of Secondary Endpoints

ORR
Subjects in the axicabtagene ciloleucel arm had statistically significantly higher objective ORR compared with subjects in the SOC arm. The ORR was 83% (95% CI: 77.1%, 88.5%) for the axicabtagene ciloleucel arm and 50% (95% CI: 42.7%, 57.8%) for the SOC arm, with a difference in ORR of 33.1% (95% CI: 23.2, 42.1), and the Cochran-Mantel-Haenszel (CMH) test p-value < 0.0001. The compete response (CR) rate in the axicabtagene ciloleucel arm and the SOC arms were 65% (95% CI: 57.6%, 71.9%) and 32% (95% CI: 25.6%, 39.8%), respectively, and PR rates were 18% (95% CI: 13.0%, 24.8%) and 18% (95% CI: 12.6%, 24.3%), respectively (Table 7).

Table 7. ORR and Best Overall Response per Central Assessment

Response Category	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)

Number of objective responders (CR + PR), n (%)	150 (83)	90 (50)
95% CI for ORR	(77.1, 88.5)	(42.7, 57.8)
Difference in ORR (95% CI)	33.1 (23.2, 42.1)	
Stratified CMH test two-sided p-value	<.0001	
Complete response, n (%)	117 (65)	58 (32)
95% CI for response rate	(57.6, 71.9)	(25.6, 39.8)
Partial response, n (%)	33 (18)	32 (18)
95% CI for response rate	(13.0, 24.8)	(12.6, 24.3)
Stable disease, n (%)	5 (3)	33 (18)
Progressive disease, n (%)	21 (12)	38 (21)
Undefined/no disease, n (%)	0 (0)	4 (2)
Not done, n (%)	4 (2)	14 (8)

(Source: FDA statistical reviewer)

OS

Per protocol, an interim on OS was conducted when the final analysis of the EFS and the analysis of ORR was statistically significant. The stratified log-rank test leads to a two-sided p-value=0.0317, which is greater than 0.00873, the significance level based on alpha spending function of the rho family (rho=6), therefore, no statistically significant result can be claimed for OS at this interim analysis.

The median OS was not reached for axicabtagene ciloleucel arm and 25.7 months (95% CI: 17.6, NE) for the SOC arm, with a stratified hazard ratio of 0.708 (99.2% CI: 0.460, 1.088). The percentages of patients survival at 12 months were 76.0% (95% CI: 69.1, 81.6) and 63.4% (95% CI: 55.8, 70.1), respectively (Table 8, Figure 5).

However, the interpretation of the OS results is complicated by the cross-over events: 100 subjects (56%) in SOC arm later received axicabtagene ciloleucel as new lymphoma therapy.

Table 8. Overall survival

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N = 179)**

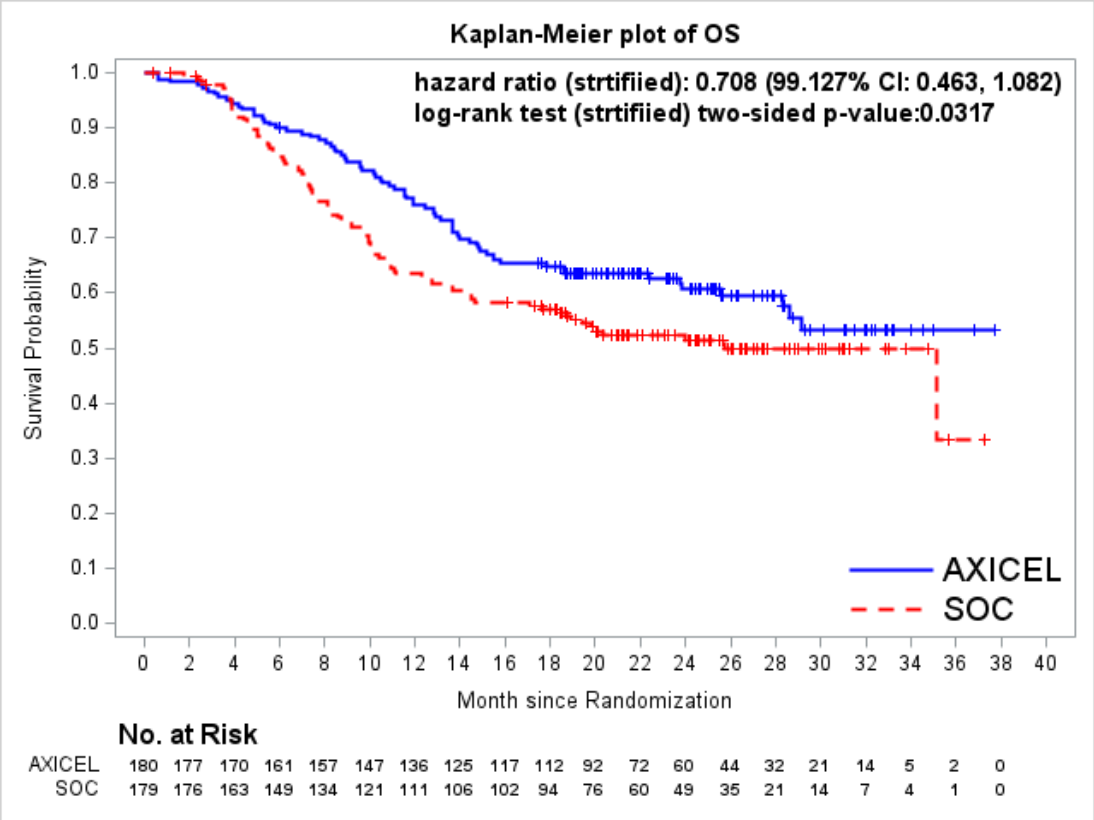
Number of subjects	180	179
Death from any cause, n (%)	72 (40)	85 (47)
Alive, n (%)	106 (59)	86 (48)
Full consent withdrawn	0 (0)	6 (3)
Lost to follow up	2 (1)	2 (1)
Stratified log-rank test, two-sided p-value	0.0317[1]	
Hazard ratio (99.127% CI)[2], stratified	0.708 (0.463, 1.082)	
KM median (95% CI)	NR (28.3, NE)	25.7 (17.6, NE)
Survival rate % (95% CI)		
3 month	96.7 (92.7, 98.5)	97.7 (94.1, 99.1)
6 month	90.0 (84.6, 93.6)	85.2 (79.0, 89.6)
9 month	83.9 (77.6, 88.5)	72.6 (65.3, 78.6)
12 month	76.0 (69.1, 81.6)	63.4 (55.8, 70.1)

1. not significant compared with p-value boundary for early efficacy claim of 0.00873
2. The two-sided alpha level allocated for this interim analysis was 0.00873

Data cutoff=March 18, 2021

(Source: FDA statistical reviewer)

Figure 5 Kaplan-Meier plot of OS



(Source: FDA statistical reviewer)

This OS analysis is based on updated OS data the applicant provided in response to FDA's information request.

Because the time to reach 250 EFS events was longer than estimated, the first interim OS analysis was conducted at 157 OS events, which was close to the timing of the planed second interim analysis for OS. As a result, the second interim OS analysis, which was scheduled at 160 events, was canceled. The applicant also changed the alpha spending function from the Lan-DeMets spending function of the O'Brien-Fleming type to the rho family (rho=6) spending function of in protocol amendment #5 (June 2020). By either spending function, at the 75% information fraction, the OS outcome did not cross the interim stopping boundary, i.e. the difference between two survival curves did not reach statistical significance at the interim.

PFS (central assessment)

PFS was statistically significantly longer with axicabtagene ciloleucel than with SOC. The median EFS was 14.9 months (95% CI: 7.2, NE) and 5.0 months (95% CI: 3.4 to 8.5), respectively, with a stratified hazard ratio of 0.562 (95% CI: 0.414 to 0.762) and a stratified log-rank test two-sided p-value=0.0002. The percentages of patients progression-free at 12 months were 53.6% (95% CI: 45.8, 60.7) and 32.3% (95% CI:

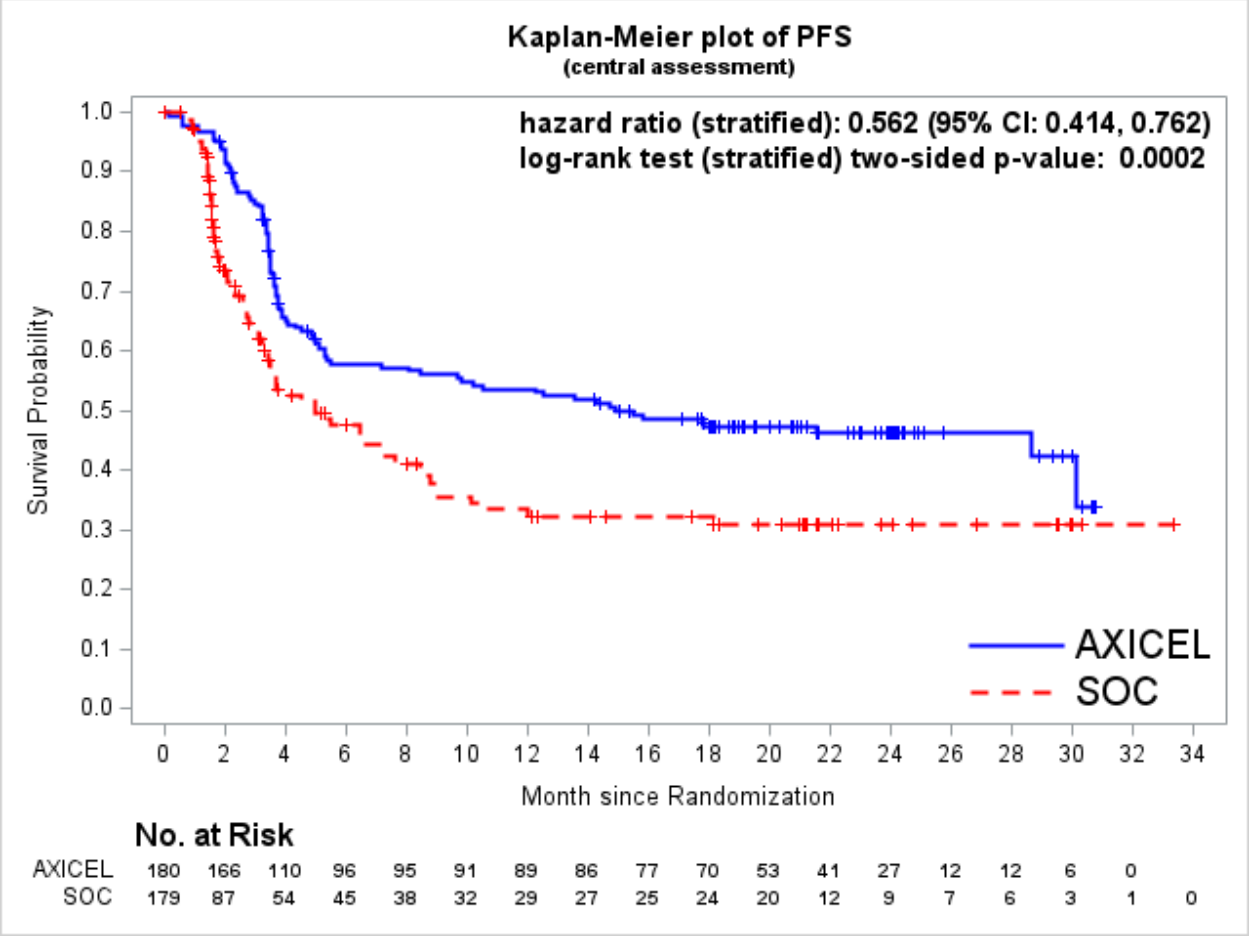
23.5, 41.4) for the axicabtagene ciloleucel and SOC groups, respectively (Table 9, Figure 5).

Table 9. PFS per Central Assessment (FAS)

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N = 179)**
Number of subjects	180	179
Events, n (%)	93 (52)	81 (45)
Censored, n (%)	87 (48)	98 (55)
Hazards ratio (95% CI), stratified	0.562 (0.414, 0.762)	
Stratified log-rank test, two-sided p-value	0.0002	
KM median (95% CI) PFS time (months)	14.9 (7.2, NE)	5.0 (3.4, 8.5)
Events		
Disease progression, n (%)	82 (46)	75 (42)
Death from any cause, n (%)	11 (6)	6 (3)
Censoring reason		
Response ongoing, n (%)	76 (42)	28 (16)
New lymphoma therapy, n (%)	9 (5)	61 (34)
Subsequent stem cell transplant, n (%)	0 (0)	2 (1)
Axicabtagene ciloleucel retreatment, n (%)	2 (1)	0 (0)
Response assessed but no disease at baseline and post-baseline, n (%)	0 (0)	3 (2)
No post-baseline disease assessment, n (%)	0 (0)	1 (1)
Full withdrawal of consent, n (%)	0 (0)	1 (1)
Lost to follow up, n (%)	0 (0)	2 (1)
Progression-free rate, % (95% CI) by KME		
3 month	84.7 (78.5, 89.3)	62.9 (53.9, 70.6)
6 month	57.8 (50.1, 64.8)	47.5 (38.2, 56.3)
9 month	56.0 (48.3, 63.1)	35.6 (26.6, 44.7)
12 month	53.6 (45.8, 60.7)	32.3 (23.5, 41.4)

(Source: FDA statistical reviewer)

Figure 6 Kaplan-Meier plot of PFS (central assessment)



(Source: FDA statistical reviewer)

Reviewer comment #2:
Table 9 shows axicabtagene ciloleucel arm had higher proportion of disease progression (46% vs. 42%) and higher proportion of death (6% vs. 3%) compared with SOC arm. However, in Figure 6 the KM curve for axicabtagene ciloleucel arm is on top of that for the SOC arm, indicating that axicabtagene ciloleucel was superior in that it delayed PFS events compared with SOC. Also, censoring for the axicabtagene ciloleucel arm tended to appear in the tail part of the KM curve due to ongoing responses, whereas censoring happened more frequently at the beginning of the KM curve for the SOC arm due to administration of new lymphoma therapy.

DOR
150 subjects (83%) in the axicabtagene ciloleucel arm had a response of CR or PR. Among the 150 responders, the overall median duration of response was 26.9 months (95% CI: 13.6, NE), and the percentage of subjects who remained in response at 12 months was 60.9% (95% CI: 52.4, 68.4), which was mainly driven by the complete responders. The median duration of response for complete responders was 28.4 months (95% CI: 26.9, NE) and only 1.6 months (95% CI: 1.4, 1.9) for the partial responders.

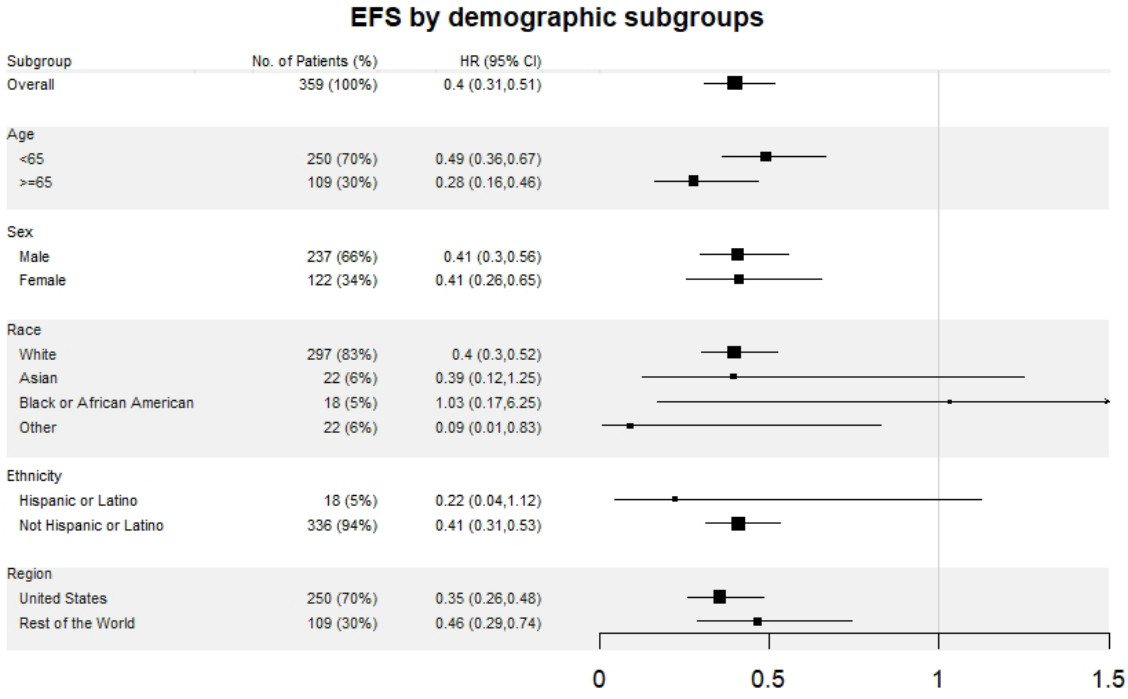
The percentage of subjects who remained in response at 12 months was 72.2% (95% CI: 63.1, 79.5) for the complete responders and 12.6% (95% CI: 3.2, 28.5) for the partial responders.

90 subjects (50%) in the SOC arm had a response of CR or PR. Among the 90 responders, the overall median duration of response was not reached, and the percentage of subjects who remained in response at 12 months was 47.6% (95% CI: 35.2, 58.9). Similar to the axicabtagene ciloleucel arm, continued response was mainly driven by the complete responders.

6.1.11.3 Subpopulation Analyses

The EFS result appears to be consistent across sex, race, ethnicity, age category, and geographic region (Figure 7). The hazard ratio in the Black or African American subgroup is slightly above 1 (1.03), however, the sample size in this racial subgroup was too small to make any conclusion.

Figure 7. EFS by age group, ethnicity, race, sex and geographic region (full analysis set)



(Source: FDA statistical reviewer)

The applicant reported that the EFS result appears to be consistent across major baseline disease characteristics, including response to first-line therapy, second-line age-adjusted IPI score, baseline ECOG, response to first line therapy, and disease type.

6.1.11.4 Dropouts and/or Discontinuations

Eight subjects in the axicabtagene ciloleucel arm died before receiving axicabtagene ciloleucel and 7 subjects in the SOC arm discontinued before receiving any salvage chemotherapy due to death (1 subject), full consent withdrawn (5 subjects), or lost to follow-up (1 subject).
At the data cutoff date, 66 subjects in the axicabtagene ciloleucel arm who received axicabtagene ciloleucel and 86 subjects in the SOC arm who received at least 1 dose of salvage chemotherapy had discontinued participation in the study. Reasons for discontinuation after receiving study therapy were:

- Death: 64 subjects, including 4 deaths due to COVID-19, in the axicabtagene ciloleucel arm; and 75 subjects, including 2 deaths due to COVID-19, in the SOC arm
- Lost to follow-up: 2 subjects in each of the axicabtagene ciloleucel and SOC arms
- Full consent withdrawn: 7 subjects in the SOC arm
- Investigator decision and other reasons: 1 subject for each category in the SOC arm

6.1.12 Safety Analyses

This section summarizes safety results of Study ZUMA-7.

6.1.12.1 Methods

Descriptive statistics are used to summarize safety data for study ZUMA-7. For data summary, the safety analysis set in this section includes 170 subjects in the axicabtagene ciloleucel treated arm who received the axicabtagene ciloleucel and 168 subjects in the SOC arm who received at least 1 dose of salvage chemotherapy.

6.1.12.3 Deaths

Among subjects in the axicabtagene ciloleucel arm, 64 subjects (38%) had died at the data cutoff date, and among subjects in the SOC arm, 78 subjects (46%) had died at the data cutoff date. Table 10 summarizes deaths for the two arms.

Table 10. Deaths reported (Safety Analysis Set)

	Axicabtagene Ciloleucel (N = 170) n (%)	**Standard of Care (N = 168) n (%)**
Subjects who died	64 (38)	78 (46)
Deaths that occurred ≤ 30 days from axicabtagene ciloleucel infusion or first dose of standard of care salvage chemotherapy	0 (0)	0 (0)
Deaths that occurred > 30 days through 3 months (92 days) from axicabtagene ciloleucel infusion or first dose of standard of care salvage chemotherapy	6 (4)	3 (2)
Deaths that occurred > 3 months (> 92 days) after axicabtagene ciloleucel infusion or first dose of standard of care salvage chemotherapy	58 (34)	75 (45)
Primary cause of death		
Adverse events	6 (4)	2 (1)
COVID-19	2 (1)	0 (0)
Progressive disease	47 (28)	64 (38)
Secondary malignancy	1 (1)	0 (0)
Other	10 (6)	12 (7)
COVID-19	2 (1)[b]	2 (1)

Data cutoff date=18Mar2021
(Source: original Table 43 CSR report body SBLA 125643/394))

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported 85 subjects (50%) in the axicabtagene ciloleuce arm and 77 subjects (46%) in the SOC arm had at least 1 SAE. The most frequently (in ≥ 5% of subjects) reported SAEs of any grade in each treatment arm were as follows:

- axicabtagene ciloleucel arm: Pyrexia (27 subjects, 16%), encephalopathy (17 subjects, 10%), hypotension (15 subjects, 9%), aphasia (9 subjects, 5%), and pneumonia (8 subjects, 5%)
- SOC arm: Febrile neutropenia (22 subjects, 13%), acute kidney injury, and pyrexia (8 subjects each, 5%)

Seventy-two subjects (42%) in the axicabtagene ciloleucel arm and 67 subjects (40%) in the SOC arm had worst Grade 3 or higher SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

The applicant reported that 157 of 170 subjects (92%) in the axicabtagene ciloleucel arm had cytokine release syndrome (CRS) of any grade; 8 subjects (5%) had worst Grade 3 CRS, 3 subjects (2%) had worst Grade 4 CRS, and no subjects had Grade 5 CRS.
The most frequently reported CRS symptoms (in ≥ 30% of subjects with CRS) were pyrexia (155 subjects, 99%), hypotension (68 subjects, 43%), and sinus tachycardia (49 subjects, 31%). The most frequently reported worst Grade 3 or higher CRS symptoms (in

≥ 5% of subjects with CRS) were hypotension (18 subjects, 11%), pyrexia (14 subjects, 9%), and hypoxia (13 subjects, 8%).

The applicant reported that 102 subjects (60%) in the axicabtagene ciloleucel arm and 33 subjects (20%) in the SOC arm had at least 1 treatment-emergent neurologic event, including 36 subjects (21%) and 1 subject (1%), respectively, with worst Grade 3 or higher neurologic events. Of these, 10 subjects (6%) in the axicabtagene ciloleucel arm had worst Grade 4 neurologic events, and no subjects in either treatment arm had a Grade 5 neurologic event.

The most frequently (in ≥ 10% of subjects) reported treatment-emergent neurologic events of any grade in the axicabtagene ciloleucel arm were tremor (44 subjects, 26%), confusional state (40 subjects, 24%), aphasia (36 subjects, 21%), encephalopathy (29 subjects, 17%), and somnolence (19 subjects, 11%).
No neurologic events occurred with a subject incidence higher than 10% in the SOC arm; the most frequently (in ≥ 2% of subjects) reported treatment emergent neurologic events in the SOC arm were paresthesia (14 subjects, 8%), delirium (5 subjects, 3%), and confusional state (4 subjects, 2%).
The most frequently (in ≥ 5% of subjects) reported worst Grade 3 or higher treatment-emergent neurologic events in the axicabtagene ciloleucel arm were encephalopathy (20 subjects, 12%), aphasia (12 subjects, 7%), and confusional state (9 subjects, 5%). One subject (1%) in the SOC arm had a Grade 3 or higher treatment emergent neurologic event of delirium.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support the efficacy and the safety of the proposed product comes from study ZUMA-7, which was a randomized, open-label, multicenter trial in adult patients with relapsed or refractory LBCL after first-line rituximab and anthracycline-based chemotherapy. In ZUMA-7, 359 patients were randomized in a 1:1 ratio to receive axicabtagene ciloleuel or SOC therapy. Randomization was stratified by response to first line therapy (primary refractory, vs relapse ≤6 months of initiating first line therapy vs relapse > 6 and ≤ 12 months of initiating first line therapy) and second line age-adjusted IPI (0-1 vs. 2-3) as assessed at the time of screening.

The primary endpoint was event-free survival (EFS), determined by blinded central review. Based on 252 EFS events, subjects randomized to receive axicabtagene ciloleucel had statistically significant improvement in EFS compared with subjects randomized to receive SOC. The median EFS was 8.3 months (95% CI: 4.5 to 15.8) for the axicabtagene ciloleucel arm and 2.0 months (95% CI: 1.6 to 2.8) for the SOC arm, with a stratified hazard ratio of 0.398 (95% CI: 0.308 to 0.514) in favor of axicabtagene ciloleucel, and a stratified log-rank test p-value<0.0001. Subjects in the axicabtagene ciloleucel arm had statistically significantly higher objective response rate (ORR) compared with subjects in the SOC arm. The ORR was 83% (95% CI: 77.1%, 88.5%) for the axicabtagene

ciloleucel arm and 50% (95% CI: 42.7%, 57.8%) for the SOC arm, with a difference in ORR of 33.1% (95% CI: 23.2, 42.1), and p-value < 0.0001based on the Cochran-Mantel-Haenszel (CMH) test. The compete response (CR) rate in the axicabtagene ciloleucel arm and the SOCT arms were 65% (95% CI: 57.6%, 71.9%) and 32% (95% CI: 25.6%, 39.8%), respectively. A planned interim analysis on OS was conducted at the time of the final EFS analysis. With 157 death occurred, which was 75% information fraction, the OS outcome did not cross the interim stopping boundary. The interpretation of the OS results was complicated by the cross-over events: 100 subjects (56%) in SOC arm later received axicabtagene ciloleucel as new lymphoma therapy.

10.2 Conclusions and Recommendations

Study ZUMA-7 met its primary efficacy endpoint: the pre-specified null hypothesis on EFS was rejected, and the key secondary endpoint of ORR was also met. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication for axicabtagene ciloleucel in this BLA Prior Approval Supplement.

Appendix. Censoring rule for EFS

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
Disease progression at planned disease assessment, prior to initiation of NALT or ASCT	Both	Event	Progression date
Disease progression in between planned disease assessments, prior to NALT or ASCT	Both	Event	Progression date
Subject with PR or CR and subsequently received NALT in the absence of disease progression	Both	Event	Last evaluable disease assessment date prior to NALT
Subject with best response of SD and subsequently received NALT in the absence of disease progression	Both	Event	Date of the first time SD was established prior to NALT
NALT in the absence of any evaluable disease assessment	Both	Event	Randomization date
Subject with best response of SD by Day 150 assessment post randomization in the absence of documented progression or death or NALT	Both	Event	Date of the first time SD was established up to and including Day 150 assessment
ASCT while in an axicabtagene-ciloleucel induced response	Axicabtagene ciloleucel	Censored	ASCT Date
Remain event-free after ASCT	SOC	Censored	Last evaluable disease assessment date
Remain event-free without ASCT	Both	Censored	Last evaluable disease assessment date
Disease progression or death after ASCT	SOC	Event	Death or PD Date
Death without documented prior event	Both	Event	Death Date
Withdrawal of consent or lost to follow-up prior to documented event	Both	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

Note: NALT = next anti-lymphoma therapy, it is defined the same as subsequent new lymphoma therapy
Note: For subjects without any evaluable disease assessment and any EFS event at the time of analysis, their EFS will be censored at the date of the randomization. Day 150 disease assessment includes any disease assessment up through the protocol specified window (+/- 14 days; up through Day 164).