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BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Supplemental BLA (SE1)
Application Number(s)	125643/394
Priority or Standard	Priority
Submit Date(s)	30 September 2021
Received Date(s)	30 September 2021
PDUFA Goal Date	01 April 2022
Division/Office	DCEPT/OTAT
Review Completion Date	01 April 2022
Established Name	Axicabtagene ciloleucel
(Proposed) Trade Name	Yescarta
Pharmacologic Class	CD19-directed, genetically modified T cell immunotherapy
Applicant	Kite Pharma, Inc.
Formulation(s)	Cryopreserved injection containing human albumin 2.5%, (b) (4) and dimethylsulfoxide (DMSO) 5%, and supplied in a patient-specific infusion bag containing approximately 68 mL
Routes of Administration	Intravenous
Dosing Regimen	Single dose with a target of 2 x 10^6 CAR-positive viable T cells/kg (maximum 2 x 10^8 cells) administered by 30-minute IV infusion and preceded by fludarabine and cyclophosphamide conditioning chemotherapy.
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Limitations of Use: Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

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OCE=Oncology Center of Excellence
MHB=Malignant Hematology Branch
DCEPT=Division of Clinical Evaluation and Pharmacology/Toxicology

Glossary

ABC	activated B cell
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Allo SCT	allogeneic stem cell transplant
AR	adverse reaction
AUC_{0-28}	area under the curve within first 28 days after axicabtagene ciloleucel infusion
auto-SCT	autologous stem cell transplant
CAR	chimeric antigen receptor
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30
eCRF	electronic Case Report Form
EQ-5D-5L	Euro-QOL, 5 Dimensions, 5 Levels
ETASU	Elements to Assure Safe Use
FAS	Full Analysis Set
FL	follicular lymphoma
GCB	germinal center B cell
HDT	high-dose chemotherapy
HGBL	high-grade B-cell lymphoma
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
ICANS	Immune effector cell-associated neurotoxicity syndrome
IR	information request
ISS	integrated summary of safety
ITT	Intent to treat
IWG	International Working Group

KM	Kaplan-Meier
LBCL	large B-cell lymphoma
LOU	limitations of use
mEFS	modified event-free survival
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NE	not evaluable, not estimable
NT	neurologic toxicity
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	preferred term
PRO	patient-reported outcome
QoL	quality of life
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab + dexamethasone, high-dose cytarabine, and cisplatin
R-ESHAP	rituximab + etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin
R-GemOx	rituximab +gemcitabine + oxaliplatin
RCR	replication-competent retrovirus
R-ICE	rituximab + ifosfamide, carboplatin, and etoposide
r/r	relapsed or refractory
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
sAAIPI	second-line age-adjusted International Prognostic Index
SAP	statistical analysis plan
SD	stable disease
SPA	special protocol assessment
SOC	standard of care, system organ class
SOCT	standard of care therapy
SUR	safety update report
TEAE	treatment-emergent adverse event
TFL	transformed follicular lymphoma
VAS	visual analog scale
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 Executive Summary

1.1. Product Introduction

Axicabtagene ciloleucel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. The clinical review team recommends regular approval of axicabtagene ciloleucel for the treatment of adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. As limitations of use (LOU), axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.

This indication is an extension of the existing indications in adult patients with relapsed or refractory (r/r) LBCL after two or more lines of systemic therapy (regular approval, October 2017) and in adult patients with r/r follicular lymphoma (FL) after two or more lines of systemic therapy (accelerated approval, March 2021). The recommended dose for the new indication remains a single infusion of 2x10e6 CAR-positive viable T cells/kg with a maximum of 2x10e8 CAR-positive viable T cells, preceded by fludarabine and cyclophosphamide for lymphodepletion.

Axicabtagene ciloleucel is engineered to recognize the transmembrane glycoprotein CD19. Critical CAR components are the anti-CD19 single-chain variable fragment and the T cell activating domains of CD3-zeta and CD28, which are all linked. When axicabtagene ciloleucel engages CD19-positive targets, the modified T cells receive signals to activate and proliferate in order to eliminate the targets. CD19 expression is restricted to the B cell lineage, present in healthy B cells, and retained by most malignancies that arise from B cells, including B-cell non-Hodgkin lymphomas.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy is based on ZUMA-7, a Phase 3, randomized, open label trial of second-line therapy of LBCL, that randomized 359 subjects in a 1:1 ratio to either a single infusion of axicabtagene ciloleucel (preceded by lymphodepleting chemotherapy) or to standard therapy. All subjects had either primary refractory disease or relapse within 12 months of completing first-line therapy, were potentially eligible for autologous HSCT, and had not yet received second-line treatment. Standard therapy consisted of protocol-defined, platinum-based chemoimmunotherapy for 2-3 cycles followed by high-dose therapy (HDT) and autologous HSCT in patients who achieved at least PR.

Overall, 74% of the study population had primary refractory disease and 26% had early relapse; diagnoses included de novo DLBCL NOS (63%), high-grade B-cell lymphoma (19%) and transformed FL (13%). Whereas 94% of the axicabtagene ciloleucel arm received CAR-T cell

infusion, 35% of the standard therapy arm underwent HSCT on protocol; lack of chemotherapeutic response was the leading reason for HSCT ineligibility.

The primary endpoint was EFS per blinded independent review committee (IRC). Key secondary endpoints were ORR per IRC and overall survival (OS). On intention-to-treat (ITT) analysis, EFS was significantly greater in the axicabtagene ciloleucel arm with a stratified HR of 0.40 (95% CI: 0.31, 0.51; stratified p<0.0001). The median EFS in the axicabtagene ciloleucel arm was 8.3 mo (95% CI: 4.5, 15.8 mo) compared to 2 mo (95% CI: 1.6, 2.8 mo) in the standard therapy arm. The estimated 18-month EFS was 41.5% (95% CI: 34.2, 48.6) and 17% (95% CI: 11.8, 23.0) respectively.

The IRC-assessed best ORR was significantly higher in the axicabtagene ciloleucel arm: 83% (95% CI: 77, 88) vs. 50% (95% CI: 43, 58) in the standard therapy arm (p<0.0001). This difference in ORR was driven primarily by a higher CR rate in the axicabtagene ciloleucel arm: 65% (95% CI: 58, 72) vs. 32% (95% CI: 26, 40) respectively. The PFS also favored the axicabtagene ciloleucel arm. The HR for IRC-assessed PFS was 0.56 (95% CI: 0.41, 0.76), translating into a median PFS of 14.9 mo (95% CI: 7.2, NE) in the axicabtagene ciloleucel arm and 5 mo (95% CI: 3.4, 8.5) in the standard arm. An interim OS analysis, performed at 75% information level, was not statistically significant. OS tended to favor axicabtagene ciloleucel, with a HR 0.71 (99.1% CI: 0.46, 1.1), p<0.03 (p-value boundary, 0.008).

In summary, ZUMA-7 provides substantial evidence of efficacy of axicabtagene ciloleucel compared to standard therapy in adult patients with primary refractory and early relapsed LBCL based on consistent improvements in EFS, PFS, ORR and CR rate and supported by interim OS data. The magnitude of the treatment effect is clinically meaningful and, coupled with the observed acceptable safety profile, is the basis for the recommended regular approval. Notably, the study was not designed to evaluate the superiority of axicabtagene ciloleucel compared to autologous HSCT in patients with first chemosensitive relapse of LBCL who are able to undergo transplantation. Hence, the clinical benefit of axicabtagene ciloleucel, as compared to HSCT, in patients with first chemosensitive relapse of LBCL is not established.

The safety of axicabtagene ciloleucel was consistent with its established safety profile. In ZUMA-7, CRS occurred in 92% of recipients (Grade ≥3, 7%) and neurologic toxicity occurred in 74% (Grade ≥3, 25%). Other Grade ≥3 adverse reactions included prolonged cytopenias (33%), febrile neutropenia (31%), and infections (14%); fatal adverse reactions occurred in 1.8%.

The recommended indication is restricted to the population that was studied: adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. The Applicant's proposed broad indication in r/r LBCL is not supported by the data. Since management of r/r primary mediastinal B-cell lymphoma (PMBCL) and other r/r LBCLs is similar, and axicabtagene ciloleucel is approved for the treatment of PMBCL after two or more prior lines of therapy, the review team did not

restrict the indication statement in this regard. As with the currently approved LBCL indication, the new indication statement includes other LBCL subtypes with few or no data, but which generally share similar treatment paradigms in the r/r setting and have a high unmet need. However, given the absence of efficacy and safety data in patients with primary CNS, the indication statement will have a LOU that axicabtagene ciloleucel is not indicated for the treatment of patients with primary CNS lymphoma. The currently approved LBCL indication has the same LOU.

In summary, ZUMA-7 represents an adequate and well-controlled study that provides substantial evidence of effectiveness and demonstrates clinical benefit in adult subjects with primary refractory and early relapsed LBCL. Given the life-threatening nature of the disease, the toxicities are acceptable. Thus, the overall benefit-risk profile is favorable and supports regular approval of axicabtagene ciloleucel for the treatment of adult patients with LBCL that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Primary refractory or early relapsed diffuse large B cell lymphoma (DLBCL) is fatal if not cured. Salvage chemotherapy regimens produce a response rate of 29% with 26% transplant rate and a 2-year EFS rate of 17%. Patients who do not respond to salvage chemotherapy have poor outcomes.	Patients with relapsed or refractory DLBCL have unmet medical needs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	HDT followed by autologous HSCT remains the standard for transplant-eligible patients with first chemosensitive relapse of DLBCL; the optimal approach for primary refractory disease is not established. Overall transplant rate in the second line setting is 33% to 55%, with lack of response to chemotherapy being the most common reason for not proceeding to HSCT. At least half of the transplanted patients eventually relapse. There is no therapy with regular approval for patients with LBCL after failure of one prior therapy.	Patients with primary refractory LBCL and early relapse of LBCL have limited effective treatment options and have an unmet medical need.
Benefit	An open label multicenter trial (ZUMA-7) randomized 359 subjects with primary refractory or early relapsed (within 1 year of first-line chemoimmunotherapy) LBCL to axicabtagene ciloleucel arm or standard therapy (salvage chemotherapy followed by HDT and autologous HSCT in responders). • The risk of an EFS event per IRC in the axicabtagene ciloleucel arm was significantly reduced compared to the SOC arm with a stratified HR of 0.40 (95% CI: 0.31, 0.51) and stratified log-rank p-value of <0.0001. • IRC- assessed median EFS was 8.3 mo for axicabtagene ciloleucel arm compared to 2.0 mo for the standard therapy arm. The estimated 18-month EFS rate was 41.5% (95% CI: 34.2, 48.6) and 17% (95% CI: 11.8, 23) respectively. Median PFS was 14.9 mo (95% CI:7.2, NE) and 5 mo (95% CI:3.4, 8.5) respectively. • ORR per IRC was 83% (95% CI: 77, 88) in the axicabtagene ciloleucel arm and 50% (95% CI: 43, 58) in the standard therapy arm. CR rate was 65% (95% CI: 58, 72) and 32% (95% CI:26, 40) respectively.	Based on the improvement in EFS, ORR, CR rate and PFS in a randomized phase 3 study, axicabtagene ciloleucel has demonstrated meaningful clinical benefit compared to standard therapy in the intended patient population with R/R LBCL. As seen in the 3rd and later-line setting, durable remissions with axicabtagene ciloleucel in the 2nd line setting primarily occur in patients who achieve CR.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the axicabtagene ciloleucel arm, the median DOR was 28.4 mo (95% CI: 26.9, NE) in patients who achieved CR and 1.6 mo(95% CI:1.4, 1.9) in patients who achieved PR.	
Risk and Risk Management	• The most substantial risks of axicabtagene ciloleucel are CRS, neurotoxicity, serious infections, prolonged cytopenias and hypogammaglobulinemia. • CRS and neurotoxicity were mitigated in the trial by careful site selection and training of investigators. • There are theoretical risks for second malignancy in this genetically modified immunotherapy based on the potential for replication competent lentivirus due to the lentivirus and insertional mutagenesis	• Axicabtagene ciloleucel has an acceptable safety profile in the intended population. • A limitation of use is warranted that this therapy is not indicated for the treatment of patients with primary CNS lymphoma, given the absence of data. • The label for axicabtagene ciloleucel has boxed warnings for CRS and neurologic toxicities. • Serious infections, prolonged cytopenia and hypogammaglobulinemia are included under warning and precautions. • The risks with axicabtagene ciloleucel warrant a REMS with ETASU. The OBE reviewers are working with the Applicant to finalize the YESCARTA TECARTUS REMS with ETASU major modification.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• A post marketing registry study to evaluate the long-term safety of axicabtagene ciloleucel in r/r LBCL patients after two or more lines of therapy has completed accrual of 1500 patients and has planned 15 years follow up. Given the absence of a new safety signal in ZUMA-7, additional enrollment to this PMR study is not warranted.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

Table 1. FDA - Patient Experience Data

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Section 8.1.1, Section 8.2.6
☐	Observer-reportedoutcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

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, accounting for 4% of all new cancer cases and 3% of cancer related deaths in the United States (US) {American Cancer Society 2020, Howlader 2020}. In Europe, NHL is the 12th most common new cancer, accounting for 3% of all new cancer cases and 3% of cancer related deaths {World Health Organization (WHO) 2020}.

Large B-cell lymphoma (LBCL) is an aggressive subset of B-cell NHL, representing 30% to 40% of NHL cases {Chaganti 2016, Morton 2006, Sehn 2015}. The most common LBCL subtype is diffuse LBCL (DLBCL) (including DLBCL not otherwise specified [NOS]), which accounts for more than 80% of LBCL cases {Sehn 2021}. In 2016, the World Health Organization (WHO) introduced high-grade B-cell lymphoma (HGBL) as a new category of LBCLs {Swerdlow 2016}. HGBL represents up to 13% of LBCL cases {Rosenwald 2019, Willenbacher 2020}.

LBCL subtypes include DLBCL NOS (defined by exclusion of unique features, and further divided according to cell of origin types, germinal center B cell [GCB] and activated B cell [ABC]), and other disparate DLBCL entities with unique clinical and pathological features such as primary DLBCL of the central nervous system (CNS); primary cutaneous DLBCL, leg type; Epstein-Barr virus-positive (EBV)$^+$ DLBCL NOS; EBV$^+$ mucocutaneous ulcer; DLBCL associated with chronic inflammation; and T-cell/histiocyte-rich LBCL {Alizadeh 2000, Campo 2011, Sehn 2021}. LBCL also includes DLBCL arising from follicular lymphoma (FL), but this subtype is not included in the WHO 2016 categorization due to the classification being based on the investigator's assessment of the clinical history of FL and not solely on histopathology. HGBL comprises 2 subcategories: 1) HGBL with *MYC*, *BCL2*, and/or *BCL6* rearrangements, which is also known as double- or triple-hit lymphoma and excludes FL or lymphoblastic lymphoma; and 2) HGBL NOS, which includes LBCL that are "high-grade" and would be previously characterized as B-cell lymphoma unclassifiable, and lacks genetic features of double- or triple-hit lymphomas {Olszewski 2021, Swerdlow 2016}.

The FDA's Assessment:

In addition to the LBCL subtypes outlined above, primary mediastinal B-cell lymphoma (PMBCL) is a rare subtype of non-Hodgkin lymphoma that predominantly occurs in adolescents and young adults. It was previously considered a subtype of DLBCL. However, under the WHO 2016 categorization, it is considered a unique entity with distinct clinical and biological features. A

rituximab and anthracycline-containing regimen is generally used for upfront therapy. End of therapy FDG-PET scans are frequently used to guide decision regarding administration of consolidative radiation therapy. Similar to first relapse of DLBCL, first relapse of PMBCL is generally managed with salvage chemotherapy followed by autologous HSCT if there is adequate response, with localized radiation therapy in some cases.[1] Salvage therapy options are similar between PMBCL and other types of LBCL, with the exception of pembrolizumab being available therapy for PMBCL that is refractory or that has relapsed after 2 or more prior lines of therapy. PMBCL is a relevant consideration because it was excluded in the ZUMA-7 trial.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

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) {Flowers 2010, National Comprehensive Cancer Network 2021}. Treatment with this regimen results in 5-year and 10-year event-free survival (EFS) rates of 47% {Feugier 2005} and 35% {Coiffier 2010}, respectively, and 5-year and 10-year overall survival (OS) rates of 58% and 44%, respectively, in patients 60 to 80 years of age {Coiffier 2010}. For patients 18 to 60 years of age, R-CHOP 3-year EFS and OS rates are 79% and 93%, respectively {Pfreundschuh 2006}. While R-CHOP has improved outcomes for patients with DLBCL overall, about 10% to 15% of patients have primary refractory disease and a further 20% to 40% of patients have disease that relapses {Chaganti 2016, Green 2012}.

The optimal therapy for the first-line treatment of patients with HGBL has not been established {National Comprehensive Cancer Network 2021, Oki 2014}. A dismal prognosis has been reported for patients with HGBL treated with various chemoimmunotherapy regimens {Green 2012, Rosenwald 2019}, and there is no consensus whether regimens more intensive than R-CHOP are required. Retrospective data with more intensive regimens such as dose-adjusted rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone have shown benefit {Oki 2014, Petrich 2014}, and have also been reported as first-line treatment for HGBL {National Comprehensive Cancer Network 2021}. A recent retrospective analysis suggests rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone may not improve survival outcomes compared with R-CHOP (4-year OS rates of 49.6% and 54.5%, respectively) {Magnusson 2021}.

Standard second-line therapy in the curative setting for LBCL is comprised of rituximab and platinum-containing salvage chemotherapy followed by high-dose chemotherapy (HDT) and autologous stem cell transplant (auto-SCT) for those who are eligible {National Comprehensive Cancer Network 2021, Tilly 2015}, with a study reporting 5-year EFS of 46% and OS of 53% in patients with relapsed/refractory (r/r) NHL who received the definitive treatment (salvage

chemotherapy and HDT-auto-SCT) {Philip 1995}. The efficacy of this regimen has not been fully assessed for HGBL {National Comprehensive Cancer Network 2021, Tilly 2015} due to conflicting data from several studies {Landsburg 2017, Oki 2014, Petrich 2014, Philip 1995, Sun 2015}.

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 {Gisselbrecht 2010, Kondo 2016, Van Den Neste 2016}. Other reasons for not undergoing HDT-auto-SCT include failure to mobilize $CD34^+$ stem cells for auto-SCT {Kondo 2016}, poor performance status, organ dysfunction, comorbidities, unresolved treatment-emergent toxicities, or age (HDT-auto-SCT is typically only recommended for patients younger than 60 to 70 years of age, depending on regional guidelines) {Friedberg 2011, Kondo 2016, Tilly 2015}. Furthermore, disease progression can occur at any point preparing for or after auto-SCT {Smeland 2016} and increased risk of death is associated with auto-SCT due to early transplant-related mortality {Assouline 2020, Caballero 1997, D'Souza 2020}. Secondary malignancies, including treatment-related myelodysplastic syndrome and treatment-related acute myeloid leukemia, are also associated with HDT-auto-SCT {Darrington 1994, Howe 2003, Milligan 1999, Smeland 2016, Smeland 2015}.

Outcomes are particularly poor for patients who have primary refractory disease or early relapse after first-line therapies; further, most of these patients are not eligible for transplant due to their chemotherapy-resistant disease {Gisselbrecht 2010, Guglielmi 1998, van Imhoff 2017a, Vellenga 2008}. Published objective response rates (ORRs) to second-line chemotherapy in patients with refractory or early relapse disease range from 14% to 55% {Guglielmi 1998, Hitz 2015, Josting 2000, Matasar 2013, Seshadri 2008, Telio 2012}. For patients who do not respond to salvage chemotherapy, a median OS of 4.4 months has been reported in one study {Van Den Neste 2016}.

Outcomes are also poor for patients with higher second-line age-adjusted International Prognostic Index (sAAIPI) scores. Studies have reported significantly higher 3-year EFS for patients with an sAAIPI of 0 or 1 factors compared with those who had 2 or 3 factors (40% versus 18%, respectively) {Gisselbrecht 2010}, and significantly improved OS and progression-free survival (PFS) {van Imhoff 2017a}. A retrospective study demonstrated 4-year PFS rates for subjects with low risk (0 factors), intermediate-risk (1 factor), and high-risk (2 or 3 factors) sAAIPI of 70%, 39%, and 16%, respectively, and 4-year OS rates of 74%, 49%, and 18%, respectively {Hamlin 2003}.

In summary, many patients do not benefit from current standard of care second-line therapy. Although higher risk is associated with disease that is refractory or relapses within 12 months of first-line therapy, only 10% of all patients with r/r LBCL are estimated to have long-term survival following auto-SCT in the rituximab era {Friedberg 2011}. Thus, a need remains for alternative second-line therapies, including those with a mechanism of action independent of chemotherapy sensitivity, whether the patient relapses before or after 12 months of first-line

therapy or is deemed eligible or ineligible to receive auto-SCT before starting salvage chemotherapy.

The FDA's Assessment:
We agree with the Applicant's assessment that approximately 60% of patients with diffuse large B-cell lymphoma can attain sustained and complete remission with first-line treatment with anti-CD 20 and anthracycline containing regimen. Thirty to forty percent of patients relapse with an additional 10% having refractory disease. The long-term survival of 10% following autologous HSCT is an underestimate for patients with standard-risk, first chemosensitive relapse of DLBCL (per CORAL study,[2] below), but we agree there is an unmet medical need.

Medically-fit patients with first relapsed or primary refractory large B-cell lymphoma are treated with the goal to achieve long-term disease control/cure. Patients are generally treated with two to three cycles of platinum-containing salvage chemoimmunotherapy to reduce the disease burden and to determine if the disease is sensitive to chemotherapy. Medically fit patients who achieve a sufficient response to salvage chemotherapy (at least PR, or in some centers or disease settings, CR) standardly undergo high- dose conditioning therapy followed by autologous HSCT. The most frequently used salvage chemotherapy regimens include R-ICE, R-DHAP, R-GDP, R-ESHAP and R-Gem Ox. There is no clear evidence regarding the superiority of one regimen over another in randomized studies in terms of efficacy and ability to collect peripheral stem cells. Table-2 below outlines the efficacy of different salvage chemoimmunotherapy regimens in randomized studies for R/R DLBCL in the second line setting.

Table 2. FDA - Efficacy of Chemoimmunotherapy and HSCT in Relapsed/Refractory LBCL

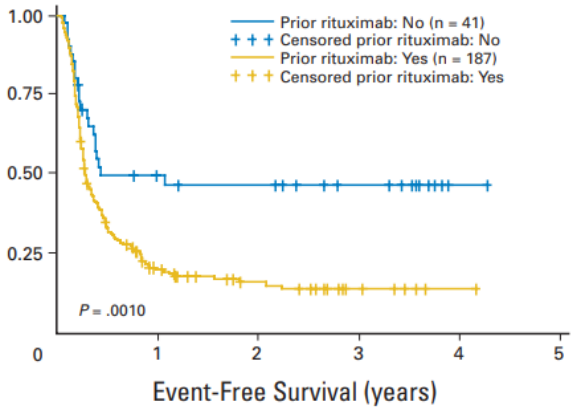
Study	High-risk	Salvage induction	N	ORR	CR rate	Transplant Rate	EFS	PFS
CORAL	54%	R-ICE	202	64%	24%	51%	3 yr 26%	3 yr 31%
		R-DHAP	194	63%	28%	55%	3 yr 35%	3 yr 42%
ORCHARRD	71%	R-DHAP	223	42%	22%	37%	2 yr 18%	2 yr 26%
		O-DHAP	222	38%	15%	33%	2 yr 16%	2 yr 24%
LY-12^	73%	R-DHAP	304	45%	15%	49%	4 yr 26%	3yr 28%
		R-GDP	306	44%	14%	52%	4 yr 26%	3yr 28%

^ LY-12 included T and B cell lymphoma. Approximately 90% of the enrolled patients had B cell lymphoma.
**High -risk disease consists of primary refractory or early relapse (within 12 mo of diagnosis for CORAL or* CR duration of <12 mo for ORCHARRD and LY-12 study).

Source: British Journal of Hematology; Volume 182, Issue 5; September 2018.[3]

In the CORAL study, in addition to 54% of the study population with refractory and early relapsed disease, approximately 61% of the patients had been exposed to rituximab. Patients with early relapse and prior rituximab exposure had inferior outcomes with 2- year EFS of about 18% (See Figure 1 below). However, for responding patients (CR or PR) who underwent HSCT, 3-year PFS was 39% compared with 14% for patients who did not receive transplantation. At a median follow up of 27 months, patients with early relapse (refractory and relapse within 12 months of diagnosis), the ORR was 46%, 3-year EFS was 20% and 3-year OS was 39%. Patients with prior rituximab exposure had ORR=51%, 3-year EFS=21% and 3-year OS=40%.[2] Mobilization failure rate of 10% was observed in both the arms. The 48-month overall survival was 48%.

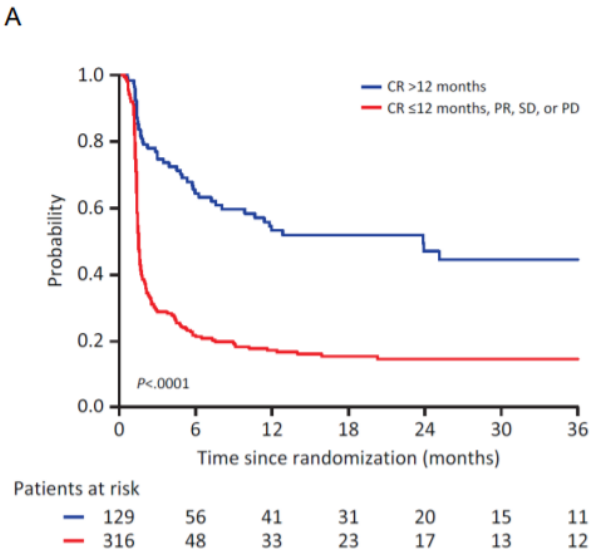
Figure 1. FDA - EFS According to Prior Rituximab and Early Relapse in CORAL Study



Source: CORAL Study; Journal of Clinical Oncology, Volume 28, Number 27, September 20, 2010.

The ORCHARRD study[4] demonstrated that subgroup of patients with high-risk disease defined as primary refractory or CR duration of <1 year to front-line therapy had an ORR of 29% with 26% completing HDT/HSCT. This compares with ORR of 67% and transplant rate of 59% for the subgroup with CR duration >1 year to front-line therapy. For the subgroup of patients that underwent transplantation on protocol, the two-year PFS was approximately 51%. Figure 2 below demonstrates the difference in prognosis based on duration of CR to front-line therapy with median PFS of 3 months in group with primary refractory and early relapse (CR duration of ≤12 mo) compared to 22 months in group with late relapse (CR duration of >12 months).

Figure 2. FDA - PFS According to Response to First-line Therapy in ORCHARRD Study



Source: Data Supplement, ORCHARRD Study, Journal of Clinical Oncology 35, no. 5, February 10, 2017.

In general, the main reason for not proceeding to HSCT in both studies was insufficient response to salvage chemoimmunotherapy.

In general, compared to primary refractory and early relapse, patients with late treatment failure are more likely to have chemo sensitive disease, respond to salvage chemotherapy and undergo HDT/HSCT. However, a proportion of patients with primary refractory and early relapsed disease may also demonstrate chemosensitivity and can have long term disease control with HSCT. Up to 25% of patients that undergo HSCT become long term survivors[5]. Overall, patients with primary refractory and early relapsed DLBCL have poor prognosis and need safe and effective treatment options.

The only therapy that is approved in the second line setting is tafasitamab in combination with lenalidomide which is under accelerated approval for the treatment of adult patients with relapsed or refractory DLBCL NOS including DLBCL arising from low grade lymphoma who are transplant ineligible. The approval was based on the results of a single arm trial that enrolled 81 patients with r/r LBCL after 1-3 prior therapies who were not candidates for HDT/HSCT. Efficacy was established on the basis of best ORR of 55% (95% CI:43%, 67%); 37% of patients had CR and 18% of patients had PR. The median duration of response was 21.7 months (range-0-24 months).[6]

No therapies are currently approved for the definitive management of r/r LBCL in the second line setting for potentially transplant eligible patients who are either primary refractory or had

early treatment failure to front-line therapy .

Several therapies are approved for patients after two or more prior lines of therapies (in the third line setting) including three CD-19 CAR T therapies: axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah) and lisocabtagene maraleucel (Breyanzi) which have regular approval. In addition, polatuzumab in combination with bendamustine and rituximab, loncastuximab tesirine and selinexor have accelerated approved for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Pembrolizumab is approved for the treatment of patients with PMBCL with primary refractory disease or disease relapsed after 2 or more prior lines of therapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

On 18 October 2017, the Food and Drug Administration (FDA) approved axicabtagene ciloleucel for the treatment of adult patients with r/r LBCL after 2 or more lines of systemic therapy, including DLBCL NOS, primary mediastinal B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from FL {YESCARTA 2020b, YESCARTA 2021}. Axicabtagene ciloleucel also received accelerated approval on 05 March 2021 for the treatment of adult patients with r/r FL after 2 or more lines of systemic therapy. On 22 April 2021, the FDA approved a Prior Approval Supplement that included safety results from the Phase 2 safety management Cohort 4 of the KTE-C19-101 (hereafter referred to as ZUMA-1) study, which assessed the effect of earlier intervention with corticosteroids and/or tocilizumab on the incidence and severity of cytokine release syndrome (CRS) and neurologic events. It is important to note that the toxicity management in KTE-C19-107, hereafter referred to as ZUMA-7, was in line with that of ZUMA-1 Cohorts 1 and 2, and not with ZUMA-1 Cohort 4 toxicity management that informed the most recently approved YESCARTA label.

The FDA's Assessment:

The LBCL indication has an LOU, that axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

FDA does not agree that management of CRS and neurotoxicity in ZUMA-7 were similar to cohorts 1 and 2 in ZUMA-1. Management of CRS and NT evolved during the conduct of ZUMA-7 with earlier intervention at lower grades of CRS and NT in ZUMA-7 compared to ZUMA-1.
On January 24, 2022, FDA approved a prior approval supplement (PAS) that included results from Cohort 6 from Study ZUMA-1, which assessed the impact of prophylactic corticosteroids

on the rate and severity of CRS and/or neurotoxicity in 39 evaluable subjects. The review of the data demonstrated that the use of prophylactic corticosteroids resulted in absence of Grade 3 or greater CRS, delayed onset of CRS and reduced the median duration of CRS. However, these benefits were offset by an increase in Grade 4 neurological toxicities and late onset of toxic/metabolic encephalopathy. Therefore, Section 5 of the USPI was updated to provide prescribers advice to administer prophylactic corticosteroids based on an individualized basis taking into consideration the benefit with regard to CRS and to weigh the risk of severe neurotoxicity. Section 2 removes advice to avoid prophylactic corticosteroids as the data from PK assessments of CAR T expansion do not suggest an inhibition of CAR T cell activity or expansion in the presence of corticosteroid administration.

Summary of Presubmission/Submission Regulatory Activity
The Applicant's Position:

Axicabtagene ciloleucel was granted Orphan Drug Designations (ODD) by the Office of Orphan Products Development for the treatment of DLBCL on 27 March 2014 (ODD # 14-4239). On 03 December 2015, the FDA granted a Breakthrough Therapy Designation to axicabtagene ciloleucel for subjects with refractory DLBCL, PMBCL, and transformed FL, and on 18 October 2017, the FDA approved axicabtagene ciloleucel for the treatment of adult patients with r/r LBCL after 2 or more lines of systemic therapy, including DLBCL NOS, PMBCL, HGBL, and DLBCL arising from FL {YESCARTA 2020b, YESCARTA 2021}. Approval by European Commission Decision followed on 23 August 2018 as a treatment for adult patients with r/r DLBCL and PMBCL after 2 or more lines of systemic therapy {YESCARTA 2020a}. Axicabtagene ciloleucel has been approved in a number of other countries, including Australia, Canada, Israel, Switzerland, Japan, and China.

ZUMA-7 was originally submitted to IND 016278 with a request for special protocol assessment (SPA) on 07 June 2017. The SPA was granted in the SPA Agreement Letter dated 11 December 2017 for clinical protocol KTE-C19 107 entitled "A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (ZUMA-7)". Formal meetings with the US FDA regarding the development of axicabtagene ciloleucel for the treatment of adult patients with r/r LBCL are listed in Table 3.

Table 3. Applicant - Formal Meetings with the Office of Tissues and Advanced Therapies Pertaining to ZUMA-7

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

Abbreviations: EFS, event free survival; LBCL, large B-cell lymphoma; r/r, relapsed/refractory; sBLA, supplemental Biologics License Application; SPA, special protocol assessment.

The FDA's Assessment:

June 7, 2017: Initial SPA for ZUMA-7 protocol was submitted.

June 30,2017: Kite agreed with Agency's recommendation to perform subgroup analyses by sex and race/ethnicity for the efficacy endpoints of EFS, ORR and OS. Kite confirmed that the primary analysis of ORR will be based on blinded central assessment and will be conducted on the FAS (full analysis set) and the primary EFS and OS analysis will be conducted on the ITT population. Kite clarified that the Day 50 tumor assessment was designed to correspond to the imaging assessment after completion of cycle 2 of chemotherapy and will assess chemosensitivity in the standard of care arm. Responders (PR or CR) will proceed to high dose chemotherapy and HSCT. Nonresponders (SD or PD) can receive additional treatment off-protocol which is considered an event and will continue on-study assessments per protocol. For the axicabtagene ciloleucel arm, Day 50 corresponds to day 21-day 28 post-infusion of CAR-T cells which is a similar time point of first post-treatment assessment compared to ZUMA-1. Kite stated that the actual and planned dose of each SOC chemotherapy administration will be captured in the e CRF including the reason for dose reduction and AEs.

July 17,2017: Agency issued non-concurrence for the SPA. The key issues for non-concurrence were related to the eligibility criteria, timing of initial efficacy assessment and assessment for overall response rate (ORR). Additional reasons for non-concurrence were related to the statistical analysis plan which was not consistent with the statistical considerations outlined in the protocol. These are further elaborated below:

1. Eligibility criteria proposed to enroll subjects who attained PR after four cycles of first line therapy as opposed to the standard of care which is up to six cycles of anthracycline based chemoimmunotherapy.

2. Lack of agreement regarding the initial assessment at day 50 post-randomization given that response in the axicabtagene ciloleucel arm may occur before day 50 while the treatment effect would occur at a later time point in the SOC arm. To ensure that the timing of first response assessment captured efficacy of 3 cycles of salvage chemotherapy, Agency recommended that sponsor revise the time of initial efficacy assessment from Day 50 to a later time point: for example, at Day 90 (following the third cycle of chemotherapy).

3. Disagreement regarding the ORR assessment which included responses only to protocol-specified chemotherapy but not to HDT/ HSCT in the SOC arm. Since the study was designed to compare the benefit of axicabtagene ciloleucel to salvage chemotherapy +HDT and HSCT, Agency recommended that ORR in the SOC include responses to HDT+HSCT. This approach would capture the PRs to salvage chemotherapy that may deepen to CRs post-transplantation. In addition, the protocol proposed that ORR be based on investigator assessment. Given the open label nature of the study, Agency recommended central blinded review of ORR to minimize bias.

July 18, 2017: Kite withdrew the request submitted for the SPA for ZUMA-7.

September 8, 2017: Teleconference was held in which Kite agreed to modify eligibility to enroll subjects who had received 6 cycles of first-line therapy unless they had no response (best response of SD or PD) after 4 cycles (primary refractory disease).
Kite agreed that ORR will capture response until observation of progression per Lugano 2014 and derivation of best response will include all assessments until an EFS event, including any assessments obtained after HSCT. Kite also agreed that all ORR assessments will be based on a central blinded review. Given that the best response at any time on the study until occurrence of an EFS event will be used to derive the ORR and not just response at Day 50, the Agency agreed with the original proposal to keep the Day 50 assessment. In addition, the Day 50 assessment had a window of 42 to 70 days to ensure that it captured tumor response 30 days after axicabtagene ciloleucel infusion and after 2-3 cycles of chemotherapy in SOC arm.
Since patients with stable disease after two cycles of salvage chemotherapy may respond to the third cycle of chemotherapy, the Agency recommended that the SOC arm should mandate three cycles of salvage chemotherapy as opposed to the proposed two cycles with the third cycle being optional. Kite highlighted that in the ORCHARRD study (van Imhoff, et al.,2017), patients assessed as SD after two cycles of salvage chemotherapy had the option to receive Cycle 3 but did not derive significant benefit. Analysis of SCHOLAR data, specifically from Ly.12 study showed that only three out of 34 patients (9%) converted from SD to PR with the optional third cycle of salvage chemotherapy. Kite provided letters from two key opinion letters to

support their position that assessment for response after two cycles is standard of care, with the third cycle being optional. The Agency considered the explanation acceptable.

October 11, 2017: Kite submitted revised protocol for ZUMA 7 under SPA.

November 20, 2017: Agency held a teleconference with the sponsor to reach agreement about EFS definition, specifically to consider subjects with stable disease in both arms as EFS events and to delay the primary analysis until Day 150 assessment is performed. Additionally, EFS definition regarding initiation of new anti-lymphoma therapy, censoring rules and timing of events needed clarification. All issues raised by the Agency were addressed and agreed upon by the sponsor.

November 22, 2017: Sponsor submitted a revised and final SPA for ZUMA-7, 3 days prior to the due date resulting in extension of the review deadline.

December 11, 2017: SPA agreement letter issued.

June 26, 2020: Kite submitted Amendment number 5 to lower the number of EFS events required to trigger primary efficacy analysis from 270 to 250 with the acceptable lower limit of 225 events. This was coupled with extending the minimum follow up for all subjects from 150 days to 9 months. This change was proposed due to the slowing of the EFS event rate starting in late 2019 and the additional concern that there will be missed assessments and deaths due to the COVID 19 pandemic that may compromise the integrity of the data. Given these considerations, the Agency accepted reduction of the EFS events from 270 to 250 as the power of the study would only decrease to 88.5% from 90.9%. However, the Agency did not agree with further lowering of the event trigger from 250 to 225 as that would result in substantial lowering of the events (from 270 to 225) and therefore may decrease the likelihood of identifying a statistically significant difference in efficacy in between the two arms in a study with important clinical implications.

August 7, 2020: In a teleconference with the Agency, Kite informed that 236 events had occurred as of August 2, 2020 and confirmed its plan to proceed with primary analysis once agreement with the Agency was reached. The Agency disagreed with the plan to lower the event trigger from 250 to 236 for the primary EFS analysis. Other key changes to the protocol included an additional interim overall survival analysis when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized, addition of time to next therapy as an exploratory endpoint , allowing for biopsy in patients who progress in standard of care arm regardless of response, and to align the pregnancy reporting requirements with other protocols sponsored by Kite. These were acceptable.

August 10, 2020: SPA-No agreement letter was issued.

August 21, 2020: Type B teleconference held for discussion of the format and content for the planned sBLA for r/r LBCL.

September 25, 2020: Sponsor submitted revised protocol Amendment 5.1 with plan for primary EFS analysis when 250 EFS events have occurred and when all subjects have been followed to Month 9 disease assessment. This change in the protocol was in alignment with Agency's feedback provided during the teleconference held on August 7, 2020.

November 25, 2020: Agency issued SPA agreement letter for ZUMA 7 Protocol Amendment 5.1.

December 2, 2020: Kite submitted Type A meeting request to discuss the timing of the primary efficacy analysis given the continued decline in the observed EFS event rate. As of November 4, 2020 (median follow up of 20.5 months), the trigger of 250 events had not occurred with total number of 237 events. The projected scenario suggested that 250 events will likely not be reached by 2022. According to the sponsor, the likelihood of obtaining a different result was low if the primary analysis was conducted at 237 compared to 250 EFS events . The sponsor requested Agency's approval regarding proceeding with the primary efficacy analyses.

February 9, 2021: During a type B teleconference held with Kite, the Agency reiterated concerns about reducing the number of events to 237 from the original agreement of 270 events for the primary efficacy analysis as it may impact the likelihood of identifying the full magnitude of treatment effect of CAR T therapy. The agency pointed out that the higher event rate observed during the initial follow up period (from September 2019 to November 2019) may be driven by the primary refractory population and a longer follow up may allow for assessment of the treatment effect in the relapsed, relatively less chemo-refractory population. In addition, Agency expressed concerns about the maturity of data due to the significant censoring between months 11-16 noted in the blinded KM EFS curves. Another concern was the post hoc modification of the target number of events for primary efficacy analysis which may introduce bias into the assessment of treatment effect. In summary, the sponsor was advised that they may proceed with the primary efficacy analysis at 237 events at their own discretion however, this will result in the invalidation of the SPA agreement dated November 25, 2020.

September 7, 2021: Type B pre-BLA teleconference held with Kite in which Agency agreed that the topline efficacy data from ZUMA-7 supported submission of pre-sBLA. The Applicant proposed a broad indication for R/R large B cell lymphoma despite no comparative efficacy data for patients who relapsed >12 months after initial therapy or for certain histological subtypes such as primary mediastinal B cell lymphoma. Feedback was provided regarding efficacy and safety datasets to be included in the datasets and handling of clinical progression as events. In addition, Agency requested clarification regarding specific censoring rules that were applied in the study.

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

4.1. Office of Compliance and Biologics Quality (OCBQ)

Not applicable for this supplement.

4.2. Product Quality

Two subjects (USUBJID (b) (6) and (b) (6)) received non-conforming lots in the axicabtagene ciloleucel arm in ZUMA-7. These two subjects were excluded from the safety analysis. Given the ITT nature of the efficacy analysis, these two subjects were included in the efficacy analysis.

4.3. Devices and Companion Diagnostic Issues

Not applicable for this supplement.

5 Summary of Nonclinical Pharmacology/Toxicology Findings

The Applicant's Position:

Reference is made to the original axicabtagene ciloleucel Biologics License Application (BLA) 125643 approved on 18 October 2017 and the subsequent supplemental Biologics License Application (sBLA) submission to BLA 125643 on 03 September 2020 (SN 0287) approved on 05 March 2021. No new nonclinical pharmacology/toxicology findings are provided with this current submission.

The FDA's Assessment:
FDA agrees with Applicant's assessment. No new nonclinical data were submitted or are in need of review in the current submission.

6 Clinical Pharmacology

6.1. Summary of Clinical Pharmacology Assessment

6.1.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The pharmacologic profile of axicabtagene ciloleucel in r/r LBCL is consistent with the known mechanism of action of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy and with previous findings in LBCL that were submitted in the original BLA (125643). Additional details are provided in Section 6.2.1.

The FDA's Assessment:
Please refer to Section 6.2.1 for FDA's assessment of axicabtagene ciloleucel pharmacokinetics/pharmacodynamics (PK/PD) data per the Clinical Pharmacology Reviewer.

6.1.2. General Dosing and Therapeutic Individualization

6.1.2.1. General Dosing

General Dosing

The Applicant's Position:

The recommended treatment regimen for patients with r/r LBCL is a lymphodepleting chemotherapy regimen of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day administered intravenously on Days −5, −4, and −3 followed by an infusion of axicabtagene ciloleucel at a dose of 2 x 10^6 anti-CD19 CAR T cells/kg body weight on Day 0. This regimen is based on aggregate safety and efficacy data from the original BLA (125643).

The FDA's Assessment:
Protocol specified dose of axicabtagene ciloleucel was target dose of 2x10e6 CAR + T cells/kg with a minimum of 1x10e6 CAR+ T cells/kg. For subjects weighing >100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x10e8 CAR+ T cells was to be administered.

6.1.2.2. Therapeutic Individualization

The Applicant's Position:

Not applicable.

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

6.1.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues.

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

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Clinical pharmacology data are provided in m5.3.4.2 Pharmacokinetics and Pharmacodynamics Report and the m272 Summary of Clinical Pharmacology.

Pharmacokinetics in Patients with r/r LBCL

The median peak anti-CD19 CAR T-cell level was 25.84 cells/µL and median area under the curve (AUC) within the first 28 days after axicabtagene ciloleucel infusion (AUC_{0-28}) was 236.23 cells/µL•days. The median time-to-peak was calculated as 8 days (ie, 7 days after the day of axicabtagene ciloleucel infusion). By Month 3, median levels of anti-CD19 CAR T-cells decreased towards baseline (0.35 cells/µL) but were still detectable in 12 out of 30 subjects until 24 months post treatment.

Numerically higher anti-CD19 CAR T-cell levels (median peak and AUC_{0-28}) were associated with subjects who had a response (complete response [CR] or partial response [PR]; 142 subjects) to axicabtagene ciloleucel treatment compared with subjects who did not respond (stable disease [SD] or progressive disease [PD]; 20 subjects). The median peak and AUC_{0-28} anti-CD19 CAR T-cell levels were higher for subjects who responded compared with those who did not respond (peak: 28.94 cells/µL versus 10.45 cells/µL, respectively; AUC_{0-28}: 292.86 cells/µL•day versus 70.14 cells/µL•days, respectively).

Pharmacodynamics

Serum Biomarkers: The serum analytes evaluated are known to be involved in mediating the antitumor activity of CAR T-cells and also play a role in CAR T-cell treatment-related toxicity

{Brudno 2018, Kochenderfer 2013, Kochenderfer 2017, Locke 2020, Neelapu 2017, Wang 2020}. Levels of analytes (proinflammatory and immune-modulating cytokines, chemokines, effector molecules, and angiogenesis and acute phase proteins) were evaluated in serum samples at multiple time points. Serum levels of the majority of these analytes increased following axicabtagene ciloleucel infusion, reaching peak levels within 8 days after infusion and returning to baseline by Week 4 after infusion. A number of these analytes were associated with CRS or neurologic event severity.

B cell levels: B-cell aplasia is an expected on-target/off-tumor pharmacodynamic effect of axicabtagene ciloleucel; thus, B-cell proportions in peripheral blood mononuclear cells (as a percentage of viable leukocytes) were monitored over time. At baseline (before lymphodepleting chemotherapy and axicabtagene ciloleucel infusion), the majority of tested subjects (81 of 141) had detectable but low B-cell levels; the median B-cell percentage in peripheral blood mononuclear cell samples was 0.27% of viable leukocytes. At Month 3, the first time point at which B cells were measured after axicabtagene ciloleucel infusion, 52 of 138 tested subjects had detectable B cells; the median percentage was 0.37%. B-cell recovery was apparent at Month 9, with the majority of subjects (45 of 77 tested subjects) presenting detectable B-cell levels and a median detectable level of 9.79%. B-cell level recovery continued through Month 24.

The Applicant's Position:

The pharmacokinetic and pharmacodynamic profiles were largely consistent with the known mechanism of action of axicabtagene ciloleucel and with previous findings that were submitted in the original BLA (125643) for subjects with r/r LBCL after 2 or more lines of therapy (ZUMA-1).

The FDA's Assessment:
Below is the summary of axicabtagene ciloleucel Pharmacokinetics/Pharmacodynamics (PK/PD) data per the Clinical Pharmacology Reviewer:

Pharmacokinetics:

- For PK analysis, blood samples were collected prior to initiation of LD, pre-infusion (baseline) and at 1, 3, 7, 14, 28 days, 3, 6, 9, 12, 18, and 24 months post-infusion with the approved dose of 2x10e6 CAR+T cells/kg and a maximum flat dose of 2x10e8 CAR+ T cells. After the initial single dose infusion of axicabtagene ciloleucel, CAR T cells exhibited an initial rapid expansion phase followed by bi-phasic decline. After infusion on Day 0, peak level in peripheral blood was achieved around Day 7 (range 2 to 233 days).

- At data cut-off date, axicabtagene ciloleucel was persistent in some subjects up to 24 months post-infusion demonstrating long term persistence.
- Higher exposure of axicabtagene ciloleucel (AUC_{0-28d} and Cmax) was observed in responding subjects [complete response (CR) + partial response (PR)], compared to non-responding subjects [stable disease (SD) + progressive disease (PD)].
- Higher exposure of axicabtagene ciloleucel (AUC_{0-28d} and C max) was observed in subjects with Grade 2 or higher CRS and Grade 3 or higher neurologic toxicity compared to lower grade toxicities.
- Higher exposure of axicabtagene ciloleucel (AUC_{0-28d} and C max) was observed in subjects administered tocilizumab and/or corticosteroids for management of CRS and/or neurologic toxicity (NT) compared to subjects who did not receive tocilizumab and /or corticosteroids for management of CRS and/or NT. Axicabtagene ciloleucel continued to expand in subjects who received tocilizumab and corticosteroids after infusion.

Pharmacodynamics:
B-cell aplasia was observed in 43% of the evaluable subjects at baseline (60 out of 141). At Month 3 post-infusion, the percentage of subjects with B-cell aplasia increased to 62% of the evaluable subjects. B-cell recovery was observed at Month 9 post-treatment and continued through Month 24.

Serum analytes (cytokines, chemokines, and immune effector-related biomarkers) generally peaked within 7 days after axicabtagene ciloleucel infusion and decreased to baseline levels by week 4 post-treatment. Following associations were observed between serum analytes levels and severe adverse events (CRS and neurological events):

• After axicabtagene ciloleucel infusion, substantially higher peak serum levels were observed in subjects with Grade 3 or higher CRS compared to subjects with Grade 2, Grade 1 or no CRS for the following biomarkers: CXCL10, ferritin, granzyme B, ICAM-1, IL-2Rα, IL-6, IL-10, IL-15, VCAM-1, GM-CSF, IL-17 and MCP-1.
• After axicabtagene ciloleucel infusion, substantially higher peak serum levels were observed in subjects with Grade 3 or higher neurologic events compared to subjects with Grade 2, Grade 1 or no neurologic events for following biomarkers: CXCL10, ferritin, granzyme B, ICAM-1, IFN-γ, IL-2Rα, IL-6, IL-10, IL-15, VCAM-1, and GM-CSF.

CSF Pharmacodynamic Biomarkers:

Compared to subjects who experienced Grade 2, Grade 1, or no neurologic events after infusion, subjects with Grade 3 or higher neurologic events had ≥ 2-fold higher CSF levels of CRP, ferritin, granzyme B, IFN-γ, IL-2Rα, MCP-1, and SAA.

Reviewer comment:
Overall, higher axicabtagene ciloleucel exposure is associated with a higher likelihood of response and with higher grade of CRS and NT. In addition, the analyses of CRS and NT effects and tocilizumab and corticosteroids use on axicabtagene ciloleucel exposure only show an association and not a causal relationship. Thus, it is unclear whether the subjects who received tocilizumab and corticosteroids have a higher exposure because of the medications or if subjects with higher exposure have worse CRS and NT that required the use of tocilizumab and corticosteroids.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Evaluation of the efficacy of axicabtagene ciloleucel as a second-line therapy in subjects with r/r LBCL in comparison with standard of care therapy (SOCT) is based on the pivotal ZUMA-7 study, based on the primary analysis data cutoff (18 March 2021). This Phase 3, randomized, open-label study evaluated the efficacy and safety of axicabtagene ciloleucel versus SOCT in subjects with r/r LBCL.

The primary evaluation of the safety of second-line axicabtagene ciloleucel is based on ZUMA-7. Supporting evidence for the safety of axicabtagene ciloleucel is provided by ZUMA-1, and the pooled axicabtagene ciloleucel population of ZUMA-7 and ZUMA-1. The FDA and EC approvals of axicabtagene ciloleucel were based on the results of ZUMA-1, which is a single arm, multicenter study in adult subjects with refractory aggressive LBCL. At the time of the original submission, ZUMA-1 comprised 2 phases: Phase 1 and Phase 2 Cohorts 1 and 2. While the scope of ZUMA-1 has increased since the original submission, safety data presented in the summary of clinical safety are from the 108 subjects treated with axicabtagene ciloleucel in Phase 1 and Phase 2 Cohorts 1 and 2. By the date of data cutoff, all subjects in ZUMA-1 have had the opportunity to be followed-up for ≥ 54 months after their infusion of axicabtagene ciloleucel (based on a data cutoff date of 18 March 2021).

Details of the studies that support efficacy and safety for the application are summarized in Table 4.

Table 4. Applicant - Listing of Clinical Trials Relevant to this sBLA

Study Identity	NCT Number	Study Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Primary Study to Support Efficacy and Safety								
KTE-C19-107 (ZUMA-7)	NCT03391466	Phase 3, active-controlled, randomized, open-label; efficacy and safety; multicenter	3 day lymphodepleting chemotherapy regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day on Treatment Days −5 to −3 followed by 2 rest days (before axicabtagene ciloleucel infusion on Treatment Day 0) at a target dose of 2 × 10^6 anti CD19 CAR T cells/kg body weight. Salvage chemotherapy; generally consisted of drugs that are not cross-resistant to first line R-CHOP and	Primary: EFS (with progression events and censoring) per blinded central assessment Key secondary: ORR per blinded central assessment and OS	Axicabtagene ciloleucel was administered IV as a single infusion of CAR transduced autologous T cells. A maximum of 1 retreatment per subject was permitted per specified criteria. / For a subject who completed the long-term follow-up period, the study was to take approximately 5 or 15 years to complete as determined by randomization	359	r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy (adults)	This study was conducted at a total of 77 investigative sites in 14 countries (US, Canada, Israel, Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, United Kingdom, and Australia).

Study Identity	NCT Number	Study Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
			included a platinum-based component; recommended to start within approximately 5 days after randomization. Subjects were to receive 2 or 3 cycles of a single permitted salvage chemotherapy regimen, with 1 cycle administered every 2 to 3 weeks. After salvage chemotherapy was administered to a subject, the subject was to receive the same chemotherapy regimen for subsequent cycles.		to the SOCT or axicabtagene ciloleucel arms, respectively. Survival status to be ascertained at each clinic visit through Month 9 after which subjects were to be contacted every 3 months through Month 24, then every 6 months until Month 60.			
Studies to Support Safety								
KTE-C19-101 (ZUMA-1)	NCT02348216	Phase 1/2, open-label; safety and	3 day lymphodepleting chemotherapy	Primary (pivotal Phase 2	Axicabtagene ciloleucel was administered	108 (Cohorts 1 and 2)	r/r[a] LBCL, including DLBCL[b] not otherwise specified,	22 sites, 2 countries

Study Identity	NCT Number	Study Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
		efficacy; multicenter	regimen consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day on Treatment Days −5 to −3 followed by 2 rest days (before axicabtagene ciloleucel infusion on Treatment Day 0) at a target dose of 2 × 10^6 anti CD19 CAR T cells/kg body weight.	study): ORR (CR or PR per the revised IWG 2007 criteria {Cheson 2007}) as determined by study investigators	IV as a single infusion of CAR transduced autologous T cells. A maximum of 1 retreatment per subject was permitted per specified criteria. / For a subject who completed the long-term follow-up period, the study was to take approximately 15 years.		PMBCL, HGBL, and TFL after 2 or more lines of systemic therapy (adults) Phase 1: DLBCL, PMBCL, or TFL Phase 2: Cohort 1: refractory DLBCL Cohort 2: refractory PMBCL or TFL	

IV, intravenous; IWG, International Working Group; LBCL, large B-cell lymphoma; NCT, National Clinical Trial; No., number; ORR, objective response rate; OS, overall survival; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with the anti-CD20 monoclonal antibody rituximab; r/r, relapsed or refractory; sBLA, supplemental Biologics License Application; SOCT, standard of care therapy; TFL, transformed follicular lymphoma; US, United States.

a Protocol Amendment 5 allowed enrollment of subjects with r/r LBCL after 2 prior lines of therapy.

b In Cohorts 1 through 3, DLBCL included HGBL which was introduced by the World Health Organization as a distinct category of LBCL in 2016 {Swerdlow 2016}.

The FDA's Assessment:

FDA agrees with the Applicant's listing of clinical trials relevant to this submission.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ZUMA-7

Trial Design

The Applicant's Description:

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOCT in adult subjects with r/r LBCL (based on the WHO 2016 lymphoma categorization). 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 SOCT. Randomization was stratified by response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy, or relapse > 6 and ≤ 12 months of first-line therapy) and sAAIPI (0 to 1, or 2 to 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 SOCT 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 HDT with or without total body irradiation, followed by auto-SCT.

An independent data safety monitoring board (DSMB) was to meet every 6 months to review safety data from randomization of the first subject until the primary analysis, and to review safety and efficacy data at the time of the planned interim futility analysis of EFS. The DSMB was chartered to make study conduct recommendations based on an analysis of benefit-risk. The DSMB could have met more often as needed.

Disease response and progression were to be evaluated per the Lugano Classification {Cheson 2014}, by blinded central assessment and by the investigator. Subjects in both treatment arms were to be assessed for response and progression at the same times relative to randomization (Study Day 0): Study Days 50, 100, 150, and Month 9, then every 3 months thereafter until Month 24, and then every 6 months from Months 30 to 60. For a subject who completed the long-term follow-up period, the study was to take approximately 5 or 15 years to complete as determined by randomization to the SOCT or axicabtagene ciloleucel arms, respectively. Subsequent therapies for lymphoma treatment that were not specified in the protocol were to be recorded for each subject randomized to a treatment arm until the subject completed the

long-term follow-up period, was considered lost to follow up, withdrew consent, or died. Survival status was to be ascertained at each clinic visit through Month 9 after which subjects were to be contacted every 3 months through Month 24, then every 6 months until Month 60.

The study design of ZUMA-7 is summarized in Table 4. An overview of the study schema is provided in Figure 3.

Inclusion Criteria:

1) Histologically proven LBCL including the following types defined by the WHO in 2016 {Swerdlow 2016}:
   a) DLBCL NOS (including ABC or GCB)
   b) HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement
   c) DLBCL arising from FL
   d) T-cell/histiocyte-rich LBCL
   e) DLBCL associated with chronic inflammation
   f) Primary cutaneous DLBCL, leg type
   g) EBV^+ DLBCL
2) r/r disease after first-line chemoimmunotherapy
   a) Refractory disease defined as no complete remission to first-line therapy (subjects who were intolerant to first-line therapy were to be excluded):
      i. PD as best response to first-line therapy
      ii. SD as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP)
      iii. PR as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy
3) Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤ 12 months of first-line therapy
4) Subjects must have received adequate first-line therapy including at a minimum:
   a) An anti-CD20 monoclonal antibody unless the investigator determined that the tumor was CD20 negative, and
   b) An anthracycline-containing chemotherapy regimen
5) Intent to proceed to HDT and auto-SCT if there was response to second-line chemotherapy
6) Subjects must have had radiographically documented disease
7) No known history or suspicion of CNS involvement by lymphoma
8) At least 2 weeks or 5 half-lives, whichever was shorter, must have elapsed since any prior systemic cancer therapy at the time the subject provided consent
9) Age 18 years or older at the time of informed consent
10) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
11) Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:
   a) Absolute neutrophil count ≥ 1000/µL

b) Platelet count ≥ 75,000/µL
c) Absolute lymphocyte count ≥ 100/µL
d) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min
e) Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal
f) Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome
g) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant electrocardiogram (ECG) findings
h) No clinically significant pleural effusion
i) Baseline oxygen saturation > 92% on room air

12) Females of childbearing potential must have had a negative serum or urine pregnancy test (females who had undergone surgical sterilization or who had been postmenopausal for at least 2 years were not considered to be of childbearing potential)

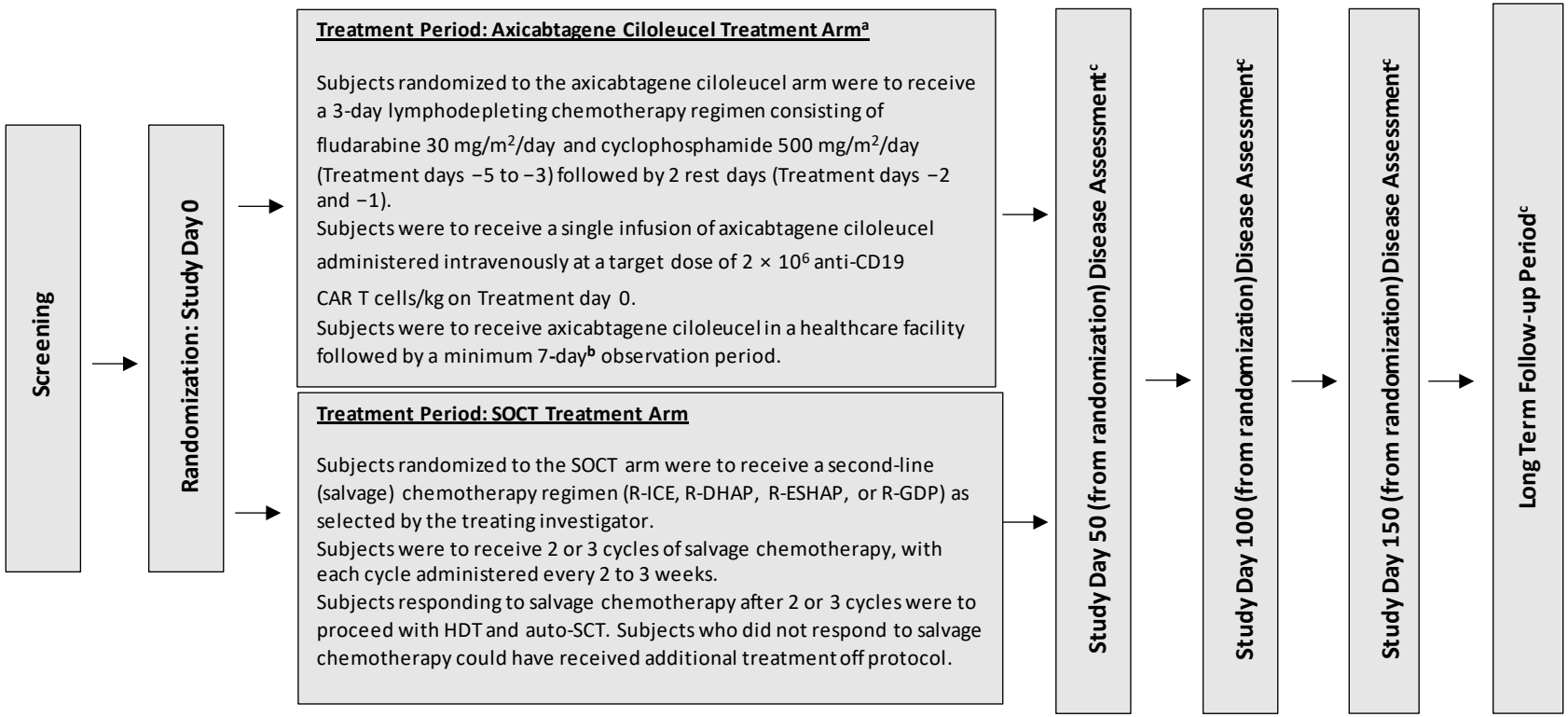
Exclusion Criteria:

1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years
2. History of Richter's transformation of chronic lymphocytic leukemia or PMBCL
3. History of auto-SCT or allogenic-SCT
4. Received more than 1 line of therapy for DLBCL
5. Prior CD19-targeted therapy
6. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 6 weeks or 5 half-lives of the drug, whichever was shorter, before the first dose of axicabtagene ciloleucel or SOCT
7. Prior CAR therapy or other genetically modified T cell therapy or prior randomization into ZUMA-7
8. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides
9. Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring intravenous antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment.
10. Known history of infection with HIV or hepatitis B or hepatitis C virus. If there was a positive history of treated hepatitis B or hepatitis C, the viral load must have been undetectable per quantitative polymerase chain reaction and/or nucleic acid testing.
11. Active tuberculosis
12. Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, were permitted.
13. Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases,

or with a history of cerebrospinal fluid malignant cells or brain metastases

14. History or presence of nonmalignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
15. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement
16. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months before enrollment
17. Requirement for urgent therapy due to tumor mass effects, such as bowel obstruction or blood vessel compression
18. History of autoimmune disease requiring systemic immunosuppression and/or systemic disease modifying agents within the previous 2 years
19. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) was allowed.
20. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months before enrollment
21. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment
22. History of severe immediate hypersensitivity reaction to tocilizumab or any of the agents used in this study
23. Treatment with a live, attenuated vaccine within 6 weeks before initiation of study treatment or anticipation of need for such a vaccine during the course of the study
24. Females of childbearing potential who were pregnant or breastfeeding because of the potentially dangerous effects of chemotherapy on the fetus or infant. Subjects of either sex who were not willing to practice birth control from the time of consent and at least 6 months after the last dose of axicabtagene ciloleucel or standard of care chemotherapy.
25. In the investigator's judgment, the subject was unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

Figure 3. Applicant - Kite ZUMA-7 Study Schema



Abbreviations: auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HDT, high-dose chemotherapy; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOCT, standard of care therapy; Study Day, number of days from the day of randomization; Treatment day, number of days from the day of axicabtagene ciloleucel treatment.

a At the discretion of the investigator, corticosteroid bridging therapy could have been considered for subjects with high disease burden at screening.

b Minimum observation period: 7 days unless otherwise required by country regulatory agencies (eg, 10 days for subjects treated in Germany, Switzerland, and France).

c Disease assessments were to be calculated from the date of randomization and not the date of dosing with axicabtagene ciloleucel or SOCT. Independent of the treatment arm, study procedures and disease assessments were to occur at the same protocol-defined time points.

Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Figure 3

The FDA's Assessment:
FDA agrees with the Applicant's description of study design, eligibility criteria and treatment outlined above. During the s BLA review, Applicant clarified that the best response to first-line therapy was defined as response at the end of first-line therapy. Therefore, subjects with a best response of CR who later developed progression during the course of first-line therapy were considered to have response of PD at the end of first-line therapy. As a result, these subjects were considered primary refractory.

In addition to the eligibility criteria at the time of screening, subjects were evaluated prior to administration of conditioning chemotherapy and axicabtagene ciloleucel to ensure candidacy for therapy. Subjects with fever, elevated CRP>100mg/L, or leukocytosis/neutrophilia prior to initiation of conditioning chemotherapy or axicabtagene ciloleucel were required to undergo work -up for any potential infection or inflammation. If any screening assessments were repeated and were outside of the eligibility criteria, then the abnormality had to resolve prior to proceeding with further therapy.

Subjects randomized to the SOC arm were required to undergo laboratory testing and assessment for AE and concomitant medication prior to each cycle of chemotherapy.

Reviewer comment:
ZUMA-7 enrolled population that was eligible for autologous HSCT. Patients in need for urgent therapy due to tumor mass effect were excluded from the study limiting the applicability of the data in patients with bulky disease needing urgent treatment.

Primary mediastinal B-cell lymphoma is a unique entity with distinct clinical and biological features. In addition to salvage chemotherapy, patients with relapsed or refractory primary mediastinal B- cell lymphoma are sometimes treated with localized radiation therapy which would be considered an event in this study and could have confounded efficacy assessment. Therefore, these patients were excluded from the study. In addition, it is noted that pembrolizumab is approved for the treatment of primary refractory mediastinal B- cell lymphoma which could also limit enrollment of this histology in ZUMA -7.

Study Design:
By the Day 50 assessment in the CAR T arm, most subjects would have received the CAR T therapy allowing for the first post-treatment response assessment. Day 50 assessment had a visit window of -7 to +21 days. In the SOC arm, this assessment was timed to capture response to 2-3 cycles of salvage chemotherapy based on which decision to proceed with HSCT was made.

The purpose of the Day 150 assessment was to capture the response assessment of the control arm after completion of salvage chemotherapy and HSCT. Based on the results of ZUMA-1

study, deepening of most responses post- axicabtagene ciloleucel occurred by Month 3 (Day 150) assessment post- treatment. Therefore, Day 150 response assessment would capture majority of responses in the axicabtagene ciloleucel arm.

The long term follow up (LTFU) in the axicabtagene ciloleucel arm is 15 years and SOC arm is 5 years. The different duration of LTFU may limit the comparative analysis in between the two arms for long term toxicities.

Study Endpoints

The Applicant's Description:

Primary endpoint: EFS (with progression events and censoring) per blinded central assessment.

Secondary endpoints:
Key secondary endpoints:

- ORR per blinded central assessment
- OS

Additional secondary endpoints:

- EFS (with progression and censoring events) based on investigator disease assessments
- PFS (with progression and censoring events) based on investigator disease assessments
- Duration of response (DOR) by blinded central assessments
- Modified EFS (mEFS)
- Incidence of adverse events (AEs) and clinically significant changes in safety laboratory test values, including antibodies to axicabtagene ciloleucel
- Changes from screening in the global health status quality of life (QoL) scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30)
- Changes from screening in the Euro-QOL, 5 dimensions, 5 levels (EQ-5D-5L) index and visual analog scale (VAS) scores

The FDA's Assessment:
Event-free survival (EFS): EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014} as determined by an independent review committee, commencement of new lymphoma therapy, death from any cause, and stable disease (SD) up to and including Day 150 assessment.

Progression free survival (PFS) is defined as the time from randomization to disease progression per Lugano Classification {Cheson 2014} as determined by investigator review or death from any cause. PFS excluded SD up to and including Day 150 assessment as an event. In addition, NALT was not considered an event but instead triggered censoring.

The independent review Committee (IRC) employed a double radiologist review paradigm where two radiologist readers reviewed each imaging time point for a subject. A single clinical reviewer reviewed the results of central radiology assessments and all available clinical data. IRC reviewers were blinded to the subject treatment arm, investigator site identifiers, subject identifiers and local radiology assessment.

Reviewer comment:
1. For the purpose of regulatory decision making, FDA has accepted EFS as primary endpoint in relapsed refractory lymphoma.
2. While the investigator assessed PFS was the protocol specified secondary endpoint, the review team recommends that PFS as assessed by the central review be considered the secondary end point to maintain consistency with the primary end point of EFS and key secondary endpoint of ORR which are based on central assessment. This would be a descriptive analysis without a formal test of statistical significance.
3. Blinded central review of efficacy assessment for both treatment arms minimized bias in ZUMA-7.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The final statistical analysis plan (SAP) version 1.0 is dated 22 June 2020 and the final supplementary SAP of patient-reported outcomes (PROs) data version 6.0 is dated 12 September 2020. The following changes in analyses or additional analyses occurred after SAP finalization:

- The primary EFS analysis was planned to occur after 250 EFS events had been observed in the study. Because the time to reach 250 EFS events was longer than estimated, the first interim OS analysis was conducted at 153 events instead of the planned 110 events. As a result, the interim OS analysis conducted at 153 events meets the criteria for both originally planned interim OS analyses at 110 and 160 events. The only subsequent planned OS analysis will be the primary (final) OS analysis, expected to occur when 210 events are observed or no later than 5 years after the first subject is randomized.
- PFS based on central assessment was analyzed with the same methods per investigator assessment, as well as in subgroups defined by baseline characteristics and presented in data tables.
- Modifications within some categories of baseline characteristics and subgroup covariates occurred.
- HDT related treatment-emergent adverse events (TEAEs) (for the SOCT arm) are provided in data tables in addition to the SAP-specified salvage chemotherapy-related and auto-SCT-related TEAE tables.

The following clarifications to definitions were made after SAP finalization:

- Concordance between EFS determined by central and investigator assessment was determined using EFS events instead of progression events.
- Therapy day 0 is used in select data tables and listings in the following instances:
  - -When referring to the day of administration of the first dose of salvage chemotherapy in the SOCT arm.
  - -In tables, listings, and narratives that use one term to refer to the day of administration of the first dose of either axicabtagene ciloleucel in the axicabtagene ciloleucel arm or salvage chemotherapy in the SOCT arm.
- The definition of the QoL analysis set in the data tables was aligned with the definition provided in the Supplemental PRO SAP as subjects who had a baseline and at least 1 completed post-randomization measurement through the Study Day 150 visit.
- The definition of bone marrow failure was aligned with the axicabtagene ciloleucel Investigator's Brochure and is therefore not identified as a potential risk of axicabtagene ciloleucel.

The statistical hypothesis of ZUMA-7 was that axicabtagene ciloleucel will prolong EFS compared with SOCT in adult subjects with r/r LBCL. The hypothesized treatment effect corresponds to a 50% improvement in the median EFS time, corresponding to a hazard ratio of 0.67.

Sample Size Considerations

The primary analysis was planned to occur when all subjects had had the opportunity to be followed for the Month 9 disease assessment (i.e., the Month 9 time point had passed for all subjects) and 250 EFS events by blinded central assessment had been observed; the study was sized to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS (the hypothesis for this study). Further, assuming a concave accrual distribution with 50% of accrual in the last 33% of the accrual period of 24 months and a 10% rate of loss to follow-up (5% by Month 1 and cumulative 10% by Month 8) in the axicabtagene ciloleucel arm and 15% rate of loss to follow-up (10% by Month 1 and cumulative 15% by Month 8) in the SOCT arm, it was anticipated that the event goal would be achieved if 350 subjects were randomized (175 subjects per arm) and would occur approximately 31 months after the first subject was randomized.

Control of Type I Error

The study was planned to have an overall alpha (significance level) of 2.5% with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints were to follow a hierarchical scheme:

- First, EFS was to be tested at the primary analysis. An EFS hazard ratio (HR) (test versus

control arm) of 0.67 was hypothesized. Assuming an exponential distribution for EFS and a median EFS of 4 months in the SOCT arm, this implied a 50% relative improvement in EFS, corresponding to a median EFS of 4 versus 6 months (control versus test arm, respectively). Log-rank test stratified by randomization factors were to be used to test the null hypothesis of no difference in EFS using an overall 1-sided alpha level of 2.5%.

- Conditional on a statistically significant improvement in EFS, ORR was to be tested at the 1-sided alpha level of 2.5% at the time of the primary EFS analysis. ORR was to be tested with a stratified Cochran-Mantel-Haenszel (CMH) test using randomization factors.
- Conditional on a statistically significant improvement in EFS and ORR, OS was to be tested up to 3 times at an overall alpha level of 2.5%. The primary analysis of OS is to occur when approximately 210 deaths have been observed or no later than 5 years after the first subject was randomized, with a first interim analysis of OS scheduled to occur at the time of the primary EFS analysis (at a 52% information fraction corresponding to 110 events) and second interim analysis occurring when approximately 160 deaths have been observed or no later than 4 years after the first subject was randomized (at a 76% information fraction corresponding to 160 events). A spending function of the Rho family with parameter (Rho = 6) was to be used to allocate the alpha between the 2 interim analyses of OS and the primary analysis of OS. Log-rank tests stratified by randomization factors were to be used to test the null hypothesis of no difference in OS.

(b) (4) software (b) (4) was used to evaluate the operating characteristics of this design.

If a statistically significant improvement in EFS was not demonstrated at the time of the primary EFS analysis, hierarchical testing of ORR and OS was not to occur. If a statistically significant improvement in EFS was demonstrated, but a statistically significant improvement in ORR was not demonstrated at the time of the primary EFS analysis, hierarchical testing of OS was not to occur.

The FDA's Assessment:
Please refer to statistical review memo for details.

The following criteria were used to further define events and event times:

- Subjects with established PR or CR who subsequently commence new anti-lymphoma therapy (NALT) including radiotherapy, except for TBI used as conditioning for HSCT in SOC arm in the absence of documented disease progression will have EFS time defined as the time from randomization to the last evaluable disease assessment prior to the new anti-lymphoma therapy.
- Subjects with best response of SD and subsequently commence new anti-lymphoma therapy (including radiotherapy, except for TBI as noted above) in the absence of documented disease progression will have EFS time defined as the time from randomization to the first time SD was established prior to the new anti-lymphoma therapy.

- Subjects who commence new anti-lymphoma therapy (including radiotherapy, except for TBI as noted above) in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date.
- Subjects with best response of SD up to and including Day 150 assessment post randomization will be considered to have an EFS event. For such subjects, the EFS time will be defined as the time from randomization to the first time SD was established up to and including the Day 150 disease assessment.

The following criteria were used to define the censoring times:

- Subjects alive, in response, and with no new therapy will be censored at the last evaluable disease assessment.
- Subjects with no evaluable disease assessment by Day 150 assessment post randomization will not be considered to have an EFS event, and the EFS time will be censored at the randomization date.
- The EFS time for subjects in the axicabtagene ciloleucel arm who undergo HSCT in the absence of any documented progression or new therapy will be censored on the day of HSCT.
- For subjects in the SOC arm, TBI, HDT, and HSCT that occur while the subject is in response from protocol-specified induction therapy will not be considered an EFS event. The EFS time for SOC arm subjects alive, progression-free, and with no new anti-lymphoma therapy will be censored at the last evaluable disease assessment date.

For the primary analysis of EFS, disease progression events and censoring times will be determined by blinded central review. Events of new therapy and death will be based on the clinical trial database.

Reviewer comment:

1. The purpose of considering SD up to and including Day 150 assessment as an EFS event as opposed to SD attained at an earlier timepoint was to allow for completion of the third cycle of chemotherapy in the SOC arm in case of delay due to toxicity and to allow for deepening of response (conversion of SD to CR/PR) prior to declaring an event in the axicabtagene ciloleucel arm. To support this event definition, Applicant provided analysis from ZUMA 1 in which out of 25 subjects who were initially assessed with SD, 14 subjects improved to CR or PR; 11/14 subjects (79%) improved at the Month 3 disease assessment. Only two subjects (14%) improved at Month 6 and one subject (7%) at one year. Since SD event that does not convert to CR or PR by Day 150 does not represent a clinical benefit, the timing of the event was clocked back to when SD was first determined to avoid a trial design error that allows for the time to event to be extended solely in the investigational arm. This

would allow for balance in timing of determination of SD as an event between both arms with the exception of those responses that are delayed until Day 150.

2. It is noted that for the SOC arm, switching in between protocol specified chemotherapies due to toxicity was considered an event. However, adjustment of doses of a chemotherapy regimen due to toxicity or switching from cisplatin to oxaliplatin within the DHAP regimen was not considered an event.

Protocol Amendments

The Applicant's Description:

The original protocol, dated 22 May 2017, was amended 6 times in the US; for all other regions, the protocol was amended 5 times. However, no subjects were treated until Amendment 2 (dated 21 November 2017). Amendment 3 was not submitted to any Institutional Review Boards (IRBs) or Ethics Committees (ECs), as well as any ex-US health authorities (HA); therefore, all changes made after Amendment 2 and Amendment 4 were described and implemented under Amendment 4. Amendment 5 was submitted to and approved by HAs, IRBs and ECs outside of the US; no subjects were enrolled under this amendment in the US. Amendment 5.1 was subsequently submitted to and approved by the FDA and IRBs/ECs in the US. Overall, the changes made to the protocol did not impact the integrity of the study.

A summary of changes for each protocol amendment starting with Amendment 4 are provided in Table 5.

Table 5. Applicant – Summary of Protocol Amendment Key Changes

Protocol/Amendment	Date	Key Changes
Original	22 May 2017	
Amendment 1[a]	27 September 2017	See explanation above
Amendment 2	21 November 2017	See explanation above
Amendment 3[b] (submitted in the US)	16 January 2019	See explanation above
Amendment 4[b] (submitted in the US)	19 March 2019	• Broadened the definition of the time point from which the period of relapse is determined for the stratification factors from "relapse ≤ 6 months of initiating first-line therapy" and "relapse > 6 and ≤ 12 months of initiating first-line therapy" to "relapse ≤ 6 months of first-line therapy" and "relapse > 6 and ≤ 12 months of first-line therapy" where "of" indicates either from initiation or completion of first-line therapy. • Broadened the definition of the time point from which progression is determined for the inclusion sub-criterion

		"partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression" from "≤ 12 months of initiating first-line therapy" to "≤ 12 months of first-line therapy," where "of" indicates either from initiation or completion of first-line therapy • Broadened the definition of the time point from which the period of relapse is determined for the inclusion sub-criterion "relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse" from "≤ 12 months of initiating first-line therapy" to "≤ 12 months of firstline therapy," where "of" indicates either from initiation or completion of first-line therapy. • Updated the inclusion criteria to maintain alignment with the WHO lymphoid malignancy categories, wherein changes made in 2016 led to the recognition of DLBCL subtypes of T-cell/histiocyte-rich large B-cell lymphoma, EBV$^+$ DLBCL, and primary cutaneous DLBCL, leg type as unique entities and the HGBL category was created {Swerdlow 2016}. Therefore, inclusion criteria were updated from DLBCL including transformation from FL to LBCL including DLBCL, NOS; HGBL with or without MYC and BCL2 and/or BCL6 rearrangement; DLBCL arising from FL; T cell/histiocyte-rich large B-cell lymphoma; DLBCL associated with chronic inflammation; primary cutaneous DLBCL, leg type; and EBV$^+$ DLBCL. • Clarified the required duration of subject observation after axicabtagene ciloleucel infusion was to be aligned with country-specific requirements. • Aligned requirements for initiating leukapheresis, lymphodepleting chemotherapy, axicabtagene ciloleucel infusion and retreatment with the axicabtagene ciloleucel clinical study program. • Clarified the duration of the period for collecting information for concomitant therapy was to include targeted concomitant therapies from Study Day 150 until Month 12, and that recording of this information stopped at Month 12, change in lymphoma therapy, or disease progression, whichever came first. • Updated that PET-CTs were to continue through Month 9 or until a change in lymphoma therapy or disease progression, whichever came first. Clarified that imaging follow-up was to be performed for subjects who discontinued protocol therapy due to an assessment of PD,

		but for whom there was no change in lymphoma therapy. Clarified that subjects for whom CT scans with contrast were contraindicated were to undergo MRI with contrast in addition to noncontrast CT scans. • Clarified that samples of apheresis and final product were to be retained and tested to understand the mechanism of action and safety profile of axicabtagene ciloleucel. • Updated the SOA tables (for both treatment arms) to include respiratory rate as a vital sign procedure and the WPAI:GH was added to the therapy days –5 and 0 assessments to align with collection of the other PROs. The axicabtagene ciloleucel treatment arm SOA was updated with an additional blood draw for PBMCs at Treatment day 3 and the mini-mental state examination was removed as a mandatory part of the neurologic assessment. The SOCT arm SOA table was updated with additional blood draws at Cycle 1 and Study Days 50, 100, and 150 and for long-term follow-up assessments at Months 9, 12, 18, 24, 36, 48, and 60. • Added 3 time points for PRO assessment (Months 18, 21, and 24) to the long-term follow-up. • Updated the AE reporting period to post-randomization through Study Day 150 or a change in lymphoma therapy, whichever occurred first. • Updated the SAE reporting period to after signing of the informed consent through the Study Day 150 visit or until initiation of a new lymphoma therapy, whichever occurred first. The reporting period for targeted SAEs was updated to 5 years for the SOCT arm and 15 years for the axicabtagene ciloleucel arm, or until disease progression, whichever occurred first. • Described the reporting requirements for deaths to match the current axicabtagene ciloleucel clinical study program
Amendment 2 to 4 Summary of Changes[b] (submitted ex-US)	19 March 2019	See explanation above
Amendment 5 (current version ex-US)	25 June 2020	• Modified the primary EFS analysis event trigger from 270 to approximately 250 EFS events with an acceptable lower limit for the observed total EFS events of 225, which was to maintain the power for the primary analysis to within 5% of the targeted 90%.

		• Increased the required duration of follow-up for the primary analysis of EFS from the Study Day 150 assessment to the Month 9 assessment. • Added a second interim OS analysis and a sensitivity analyses of OS. The second interim analysis of OS was to occur when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized. The sensitivity analyses were added to address the confounding effect from treatment switching. • Added a time frame for the primary analysis of OS so that it was to occur either when approximately 210 deaths have been observed or no later than 5 years after the first subject was randomized. • Added TTNT as an exploratory endpoint. • Provided guidance for sites to encourage collection of a biopsy confirming disease progression and to submit the biopsied tissue to the central laboratory. • Updated the revised pregnancy and lactation reporting language to be consistent with EU requirements and to align across Kite programs. • Clarified the TEAE definition as any AE that begins on or after the first dose study treatment (axicabtagene ciloleucel infusion or standard of care salvage chemotherapy), to be in alignment with the definition used in other Kite studies.
Amendment 5.1 (current version in the US)	16 September 2020	• Reference to an acceptable lower limit for the observed total EFS events to trigger the primary analysis was removed at the request of the FDA. • Removed "approximately" from the 250 events required to trigger the primary analysis at the request of the FDA.

Abbreviations: AE, adverse event; CT, computed tomography; BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr Virus; EFS, event free survival; EU, European Union; FDA, Federal Drug Administration; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; IEC, Insitutional Ethics Committee; IRB, Institutional Review Board; LBCL, large B-cell lymphoma; MRI, magnetic resonance imaging; NOS, not otherwise specified; OS, overall survival; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PET, positron emission tomography; PR, partial response; PRO, patient-reported outcome; SAE, serious adverse event; SOA, schedule of assessments; SOCT, standard of care therapy; TEAE, treatment-emergent adverse event; TTNT, time to next treatment; US, United States; WPAI:GH, Work Productivity and Activity Impairment Questionnaire: General Health.
Notes: A communication letter were sent on 04 May 2018 to investigators to correct guidance in the protocol that all SAEs (not just Grade 3 or higher) should be submitted to Kite within 24 hours following investigator knowledge of the event and a note to

file was sent 14 May 2018 to clarify that subjects who did not respond to 2 or 3 cycles of chemotherapy should switch lymphoma therapy; both communications were reconciled in the subsequent amendment.

a This amendment was submitted to IRB/IECs but no subjects were treated on this amendment.

b Amendment 3 was only submitted to the FDA but was not sent to any IRB or IECs; therefore, no subjects were treated on this amendment. Changes between Amendment 2 and 4 were summarized for regions outside of the US.

Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 7.8

The FDA's Assessment:

The section below summarizes FDA's assessment of protocol amendments 1-4.

Protocol amendment 1: Key changes in this amendment included:

1)ORR, DOR and duration of CR as determined by blinded central review will be the secondary objective/endpoint as opposed to investigator assessment. For derivation of ORR, all assessments post-randomization and up through disease progression will be used. This includes assessments obtained after HSCT.

2)Subjects could be observed daily as outpatients for at least 7 days after axicabtagene ciloleucel infusion for AEs as opposed to mandated hospitalization.

3)Requirement was added that subjects should be instructed to remain within proximity of the clinical site for at least 4 weeks following axicabtagene ciloleucel infusion.

4)Oxaliplatin was allowed in place of cisplatin for RDHAP regimen.

5) All subjects randomized to the axicabtagene ciloleucel arm will undergo blood draws for evaluation of serum cytokines and chemokines as opposed to only subjects with CRS and NT.

6) Monitoring for RCR at baseline, Day 150 and Month 12 will be required as opposed to optional assessment.

7) Blood work for delayed AEs will be collected yearly for up to 15 years as part of LTFU.

8) Analysis of ORR will be in the ITT set as opposed to the cohort with measurable disease at baseline.

9) Clarification that interim analysis will not allow for early stopping for efficacy and that futility stopping rule is non-binding.

10) Clarification that treatment with axicabtagene ciloleucel is intended to be definitive therapy and not bridge to HSCT.

11) Subjects with PR after at least 6 cycles of front line therapy will be eligible for the study as opposed to 4 cycles of therapy if they have disease progression within 12 months from initiation of therapy

12) SAEs that are considered related to axicabtagene ciloleucel should be reported regardless of the time period and targeted SAEs and secondary malignancies will be reported for up to 15 years.

Protocol amendment 2: Key changes in the amendment include:

1) Addition of modified EFS (defined as EFS with the exception of SD at Day 150 assessment) as a secondary endpoint based on blinded central review and investigator assessment.

2) Requirement for biopsy proven residual disease in subjects with PR as best response after at

least 6 cycles for defining refractory disease.
3) Clarification that subjects who are alive and without disease progression will have continued follow up for disease progression.
4) Additional criteria were added to define events and censoring times for the primary efficacy analysis
5) Information that primary analysis of EFS will occur when all subjects have had the opportunity to be followed to Day 150 disease assessment and a minimum of 270 EFS events have been observed
6) A sensitivity analysis will be performed in which subjects in the axicabtagene ciloleucel arm who undergo HSCT while in axicabtagene ciloleucel induced response are considered to have an EFS event (with EFS time defined as time from randomization to the date of HSCT).

Protocol amendment 3:Key changes made to the protocol include:
1) Timeframe to define relapsed disease was broadened from ≤12 months of initiating first-line therapy to within 12 months of either initiation or completion of first-line therapy. Similarly, the time frame to define refractory disease as PR with PD ≤12 months of initiating first line therapy was broadened to include within 12 months of either initiation or completion of first line therapy. The applicant's rationale was based on the Phase III ORCHARRD trial in which patients with primary refractory disease or relapse ≤12 months after completion of first line therapy had lower PFS and OS compared to those who relapsed >12 months later indicating that early relapse patients do poorly regardless of the time point that is used to define early relapse such as within 12 months from diagnosis or CR or initiation or completion of first-line therapy.
2) Modification of time to define relapse for the stratification factors of ≤ 6 months and >6 and ≤ 12 months from initiation to either initiation or completion of first line therapy to keep in alignment with the broadening of the eligibility criteria.
3) Updating the definition of large B- cell lymphoma to WHO 2016 classification (Swerdlow et al, 2016) to include DLBCL NOS (ABC/GCB), HGBCL with or without MYC and BCL2 and/or BCL6 rearrangement, T cell/histiocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation, primary cutaneous DLBCL, leg type and EBV+ DLBCL.
4) Adding a new section outlining requirements for initiation of conditioning chemotherapy or axicabtagene ciloleucel infusion if there was any clinical concern for potential infection.
5) MMSE was removed as mandatory part of neurological assessment.
6) Update to clarify that PET-CTs will continue through Month 9 or until change in lymphoma therapy or PD, whichever occurs first.
7) Subjects who discontinue protocol therapy due to PD but without any new antilymphoma therapy will have central review of any subsequent imaging.
8) Reporting period for AEs and SAEs were updated to include period from signing informed consent through the Day 150 visit or until initiation of new lymphoma therapy whichever occurs first.
7) Reporting of deaths and pregnancies updated to align with all studies with axicabtagene ciloleucel

8) Clarification that for both arms, derivation of best response will include all assessments until an EFS event, including any assessment after HSCT for the SOC arm.
8) Clarification that for PFS analysis, subjects who receive NALT (with the exception of HDT,TBI for HDT and SCT while in a protocol therapy induced response) in the absence of PD will be censored at the last evaluable disease assessment prior to commencement of NALT.
9) Clarification that for primary DOR analysis, DOR will be censored at the last evaluable disease assessment date prior to SCT while in protocol therapy induced response in the axicabtagene ciloleucel arm and will be censored at the last evaluable disease assessment including assessments after SCT in the SOC arm.

Protocol amendment 4: Key changes made to the protocol include clarification that
1) For subjects weighing>100kg, maximum flat dose of axicabtagene ciloleucel at 2 x10e8 CAR+ T cells will be administered.
2) Targeted SAEs for SOC and axicabtagene ciloleucel will be collected for 5 and 15 years respectively.

The Agency agrees with changes that are summarized above for amendment #5 and 5.1.

Study Results

Compliance with Good Clinical Practices

Data:

The Kite Pharma (hereafter referred to as Kite) Quality Assurance group conducted 7 compliance audits of sites during the course of the study. No critical audit findings were observed. Site audit certificates are provided in m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report (CSR), Section 16.1.10.

The Applicant's Position:

All studies conducted in the axicabtagene ciloleucel development program met the requirement for International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines. Therefore, data should be interchangeable across regions. For studies conducted under a US Investigational New Drug Application, investigators were required to ensure that the basic principles of Good Clinical Practice (GCP) were adhered to, as outlined in Code of Federal Regulations (CFR) Title 21, Part 312, subpart D (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 5.2). These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

The FDA's Assessment:
The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

Certificates of audit for seven investigative sites that underwent compliance audits by the Applicant for this study were included in the sBLA submission.

After consideration of factors including subject enrollment, protocol deviations, financial disclosures and inspection history, three clinical sites (covering approximately 15% of subjects enrolled in full analysis set of ZUMA- 7 study) were selected for inspection and verification of submitted data by FDA's bioresearch monitoring (BIMO) team:

Site 002: Moffitt Cancer Center.
Site 039: St. Joseph Medical Center (University of Maryland Medical Center).
Site 303: Universitair Medisch Centrum Groningen – Netherlands.

Key Inspectional findings are summarized below:
Per the BIMO reviewer for Site 002: the FDA investigator discovered that some concomitant medications were not reported for four out of seven subjects. However, none of these medications were considered prohibited or exclusionary for the study and only less than 2% were not reported. The site has since created a new work-instruction for reviewing concomitant medications in the electronic medical record.

Per the BIMO reviewer for Site 039: One subject received cyclophosphamide dose based on actual body weight(ABW) as opposed to the institutional guideline of using the ideal body weight (IBW) if ABW was more than >125% of IBW. This patient did not have any unexpected toxicity and continues to be disease free. BIMO reviewer observed errors in the dose calculation form in two additional subjects, however, the correct dose of cyclophosphamide was administered to these subjects. A more efficient chemotherapy ordering module has been implemented to prevent these errors.

Per BIMO reviewer for Site 303: Several SAEs were reported late to the sponsor. The site has issued new procedures to correct this and provided a plan to the ORA investigator.

Overall, the inspections verified the data reported in the sBLA, including but not limited to subject eligibility, protocol deviations, study drug administration, primary efficacy endpoint, and adverse events for subjects enrolled at the inspected clinical sites. No significant sponsor or monitoring issues were identified during the above inspections. The financial disclosure information submitted to the s BLA was verified for each of the clinical investigator at the inspected clinical study sites.
No Form FDA 483 was issued for three sites.

Reviewer comment: The discrepancies and errors are considered insignificant from clinical perspective, and they did not impact either the results of the reviewer's analyses or conclusions.

Financial Disclosure

Data:

Kite Pharma has adequately disclosed financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Financial disclosure information is provided in m1.3.4, Financial Certification and Disclosure for investigators involved in ZUMA-7.

The Applicant's Position:

Additional details are provided in the Appendix (Section 18.2).

The FDA's Assessment:
See Section 16.2 for details.

Patient Disposition

Data:

A total of 359 subjects were randomized and included in the full analysis set (FAS), 180 subjects in the axicabtagene ciloleucel arm and 179 subjects in the SOCT arm. Of the subjects who received axicabtagene ciloleucel or SOCT, 152 subjects (42%) had discontinued from the study at the time of the data cutoff date (66 of 180 subjects [37%] in the axicabtagene ciloleucel arm and 86 of 179 subjects [48%] in the SOCT arm). The primary reason for study discontinuation was death in both the axicabtagene ciloleucel (64 subjects [36%]) and the SOCT arm (75 subjects [42%]) (m5.3.5.1, ZUMA 7 Primary Analysis CSR, Table 14.1.2).

The median actual follow-up time (from randomization to date of death or last date known to be alive) was longer in the axicabtagene ciloleucel arm (20.07 months, range: 0.59 to 37.75 months) than the SOCT arm (18.23 months, range: 0.03 to 37.26 months). Median potential follow-up time (from randomization to data cutoff) was similar in the axicabtagene ciloleucel arm (25.00 months, range: 17.48 to 37.75 months) and the SOCT arm (24.84 months, range: 17.58 to 37.26 months). All subjects in the FAS had reached ≥ 15 months potential follow-up (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 14.1.2).

Table 6 presents a summary of the disposition of subjects in ZUMA-7.

Table 6. Applicant - Disposition of Subjects in ZUMA-7 (FAS)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Subjects randomized, n	180	179	359
Axicabtagene ciloleucel			
Underwent leukapheresis, n (%)	178 (99)	NA	NA
Received bridging therapy, n (%)	65 (36)	NA	NA
Received conditioning chemotherapy, n (%)	172 (96)	NA	NA
Received axicabtagene ciloleucel, n (%)	170 (94)	NA	NA
Received retreatment axicabtagene ciloleucel, n (%)	9 (5)	NA	NA
Standard of care therapy			
Received standard of care salvage chemotherapy, n (%)	NA	168 (94)	NA
Underwent leukapheresis of $CD34^+$ stem cells, n (%)	NA	74 (41)	NA
Received high-dose therapy, n (%)	NA	64 (36)	NA
Received $CD34^+$ stem cell rescue, n (%)	NA	62 (35)	NA
Subjects who did not receive conditioning chemotherapy, axicabtagene ciloleucel, or standard of care therapy, by reasons, n (%)	8 (4)	11 (6)	19 (5)
Adverse event	2 (1)	0 (0)	2 (1)
Death	2 (1)	0 (0)	2 (1)
Disease progression	2 (1)	0 (0)	2 (1)
Subject request	0 (0)	8 (4)	8 (2)
Lost to follow-up	0 (0)	1 (1)	1 (0)
Other	2 (1)	2 (1)	4 (1)
Subjects who received conditioning chemotherapy but not axicabtagene ciloleucel by reasons, n (%)	2 (1)	NA	NA
Adverse event	2 (1)	NA	NA
Subjects who received axicabtagene ciloleucel or standard of care therapy, n (%)	170 (94)	168 (94)	338 (94)
Subjects who received bridging therapy, n (%)	60 (33)	NA	NA
Subjects who completed treatment, n (%)	170 (94)	89 (50)[a]	259 (72)
Subjects who initiated but did not complete axicabtagene ciloleucel infusion or standard of care by reasons, n (%)	0 (0)	79 (44)	79 (22)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Adverse event	0 (0)	2 (1)	2 (1)
Disease progression	0 (0)	71 (40)	71 (20)
Other	0 (0)	6 (3)	6 (2)
Primary reason for ending the study			
Subjects who did not receive axicabtagene ciloleucel or standard of care therapy, n (%)	8 (4)	7 (4)	15 (4)
Death	8 (4)	1 (1)	9 (3)
Lost to follow-up	0 (0)	1 (1)	1 (0)
Full consent withdrawn	0 (0)	5 (3)	5 (1)
Subjects who received axicabtagene ciloleucel or standard of care therapy, n (%)	66 (37)	86 (48)	152 (42)
Death	64 (36)	75 (42)	139 (39)
Due to COVID-19	4 (2)	2 (1)	6 (2)
Lost to follow-up	2 (1)	2 (1)	4 (1)
Full consent withdrawn	0 (0)	7 (4)	7 (2)
Investigator decision	0 (0)	1 (1)	1 (0)
Other	0 (0)	1 (1)	1 (0)
Follow-up time for all randomized subjects			
Actual follow-up time (months)[b]			
n	180	179	359
Mean (STDEV)	19.280 (8.865)	16.556 (9.474)	17.922 (9.262)
Median (Q1, Q3)	20.074 (12.649, 25.610)	18.234 (7.721, 24.411)	19.154 (9.823, 25.101)
Min, Max	0.59, 37.75	0.03, 37.26	0.03, 37.75
Potential follow-up time (months)[c]			
n	180	179	359
Mean (STDEV)	25.198 (5.144)	25.174 (4.868)	25.186 (5.002)
Median (Q1, Q3)	25.002 (20.682, 29.207)	24.838 (21.158, 28.616)	24.936 (20.961, 28.747)
Min, Max	17.48, 37.75	17.58, 37.26	17.48, 37.75
Subjects with ≥ 15 months potential follow-up[c], n (%)	180 (100)	179 (100)	359 (100)

Data cutoff date = 18MAR2021.

Abbreviations: COVID-19, Coronavirus disease 2019; eCRF, electronic case report form; FAS, Full Analysis Set; Max, maximum; Min, minimum; NA, not applicable; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.

Notes: In the SOCT arm, subjects who completed treatment are those who completed salvage chemotherapy (2 or 3 cycles), high-dose therapy, and stem cell transplant, or those who completed salvage chemotherapy and were assessed as stable disease at Study Day 50 without proceeding to stem cell transplant.

a For 2 subjects, the Study Day 50 disease assessments were updated by the clinical site to SD but the corresponding end of treatment eCRF was not updated.

b Actual follow-up time is calculated as (death date or last date known alive – randomization date + 1)/30.4375.

c Potential follow-up time is calculated as (the cutoff date – randomization date + 1)/30.4375.

Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 8

The Applicant's Position:

The number of subjects enrolled and treated with axicabtagene ciloleucel, and the duration of follow-up on ZUMA-7 is sufficient for an evaluation of the efficacy and safety of this treatment in subjects with r/r LBCL.

The FDA's Assessment:

Out of the 437 subjects that were screened for the study, 359 subjects were enrolled.

Axicabtagene ciloleucel arm:

1. Out of the 180 subjects that were randomized to the axicabtagene ciloleucel arm, two subjects (1%) did not proceed to the next step of leukapheresis. This was due to rapid disease progression requiring anti-lymphoma therapy in one subject and study ineligibility due to cardiac involvement by lymphoma in one subject.
2. Out of the 178 subjects that underwent leukapheresis, six subjects did not receive lymphodepleting chemotherapy due to following reasons:
    - Death in two subjects from the following: grade 5 sepsis and disease progression.
    - Exclusionary laboratory value in two subjects (Grade 2 ALT in one subject and Grade 3 hyperbilirubinemia in another subject) post leukapheresis rendering subject ineligible for conditioning chemotherapy. Hyperbilirubinemia was deemed to be secondary to disease progression.
    - One subject was deemed to be in false progression at screening.
    - Disease progression in one subject.
3. Out of 172 subjects that received lymphodepleting chemotherapy, two subjects did not receive axicabtagene ciloleucel infusion due to the following reasons:
    - One subject had Grade 3 CVA, and one subject had Grade 2 small intestinal perforation.

Overall, 94% (170/180) of the subjects randomized to the axicabtagene ciloleucel arm received axicabtagene ciloleucel as intended.

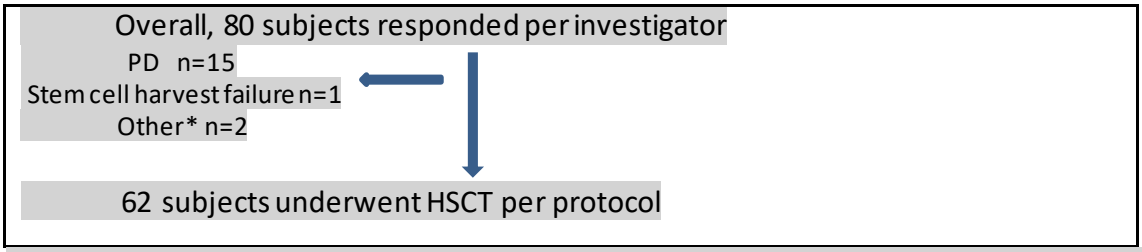
SOC Arm:

In the SOC arm, 11 subjects (6%) did not proceed to receive any chemotherapy due to the following reasons:

Eight subjects (4%) requested to not proceed with SOC arm. One subject was lost to follow up. Two subjects were found to have no evidence of active disease either on biopsy or imaging.

Out of the 168 subjects that received any chemoimmunotherapy, 80 subjects responded (48%) per investigator assessment. The disposition of these subjects is summarized below:

Figure 4. FDA - Disposition of Responders in Standard of Care Arm



*Other: one subject had a response which was considered insufficient to proceed to HDT/HSCT by investigator, one subject with response was inadvertently initiated on an alternative protocol.

For the remaining 88/168 subjects, the reasons for not proceeding with HDT/HSCT are outlined below:

Table 7. FDA - Reason for Not Proceeding in Study after Initiating Salvage Chemotherapy in 88 Subjects

Response per Investigator	N=168
Best response of disease progression	55 (33%)
Best response of stable disease	30 (18%)
Response not evaluated *	3 (2%)
Total	88 (52%)

*One subject was unable to tolerate protocol specified chemotherapy due to renal failure with initiation of off protocol therapy (bendamustine and rituximab) and two subjects switched from one protocol specified chemotherapy to another due to acute kidney injury and poor tolerability respectively prior to Day 50 disease assessment. Day 50 disease assessment post-initiation of NALT in both these subjects indicated lack of response.

Overall, 35% of the randomized subjects were able to receive definitive therapy in the SOC arm.

Reviewer comment:
1.For both the arms combined, the reverse KM estimate for the median follow up was 22.1 months (95% CI: 21.1, 23.7). This estimate excludes 70% of the study population that had an event and therefore, overestimates the actual median follow up which was 3.6 months. The potential follow up (randomization date to data cutoff) for the two arms was a minimum of 17.5 months and maximum of 37.7 months. Given that >50% of the study population had an

event at the time of primary efficacy analysis, the median EFS has been reached for both the arms. Thus, the duration of follow up in ZUMA-7 is sufficient to make a regulatory decision.

2.The study had an 82% enrollment rate which may indicate the fairly restrictive eligibility criteria for study entry. The fact that 94% of the randomized subjects were able to receive definitive therapy in the axicabtagene ciloleucel arm compared to 35% in the SOC arm highlights the multistep nature of the SOC arm and chemo refractory nature of the study population. Four percent of the enrolled subjects in the SOC arm declined to proceed with the study compared to none in the axicabtagene ciloleucel arm which could indicate subject bias against standard of care therapy possibly due to perceived lack of efficacy.

The most common reason for not proceeding with HSCT in the SOC arm was due to the lack of response to protocol specified salvage chemoimmunotherapy indicating the chemo refractory nature of the study population.

Protocol Violations/Deviations

Data:

Important protocol deviations (IPDs) were reported for 56 subjects (16%) during the study, including 31 subjects (17%) in the axicabtagene ciloleucel arm and 25 subjects (14%) in the SOCT arm; see Table 8. Each category of IPD occurred for < 10% of subjects overall. The most frequent IPD in both the axicabtagene ciloleucel and SOCT arms was missing data, (20 subjects [11%] and 10 subjects [6%], respectively).

Four subjects (1%) had an important protocol deviation due to the Coronavirus disease 2019 (COVID-19) pandemic (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 8.5.1).

Table 8. Applicant - Important Protocol Deviations (FAS)

Category	Axicabtagene Ciloleucel (N = 180) n (%)	Standard of Care (N = 179) n (%)	Overall (N = 359) n (%)
Subjects with at least one IPD	31 (17)	25 (14)	56 (16)
Due to COVID-19	3 (2)	1 (1)	4 (1)
Excluded medication	4 (2)	5 (3)	9 (3)
601 - Axicabtagene ciloleucel subject received corticosteroids or other immunosuppressive drugs within 7 days prior to leukapheresis or 5 days prior to or 6 months after axicabtagene ciloleucel related infusion	2 (1)	0 (0)	2 (1)
602 - Subject received prohibited investigational agents or radiation	2 (1)	5 (3)	7 (2)

Category	Axicabtagene Ciloleucel (N = 180) n (%)	Standard of Care (N = 179) n (%)	Overall (N = 359) n (%)
Exclusion criteria	2 (1)	1 (1)	3 (1)
202 - History of Richter'stransformation of CLL or PMBCL	0 (0)	1 (1)	1 (0)
215 - Cardiac Lymphoma Involvement	1 (1)	0 (0)	1 (0)
220 - Deep vein thrombosis or pulmonary embolism within 6 months	1 (1)	0 (0)	1 (0)
IP error axicabtagene ciloleucel	1 (1)	0 (0)	1 (0)
304 - Axicabtagene ciloleucel administered without meeting pre-infusion requirements	1 (1)	0 (0)	1 (0)
IP error axicabtagene ciloleucel rt	1 (1)	0 (0)	1 (0)
307 - Retreated with axicabtagene ciloleucel but did not meet retreatment criteria	1 (1)	0 (0)	1 (0)
Inclusion criteria	6 (3)	9 (5)	15 (4)
101 - Histologically proven DLBCL including transformation from FL	0 (0)	1 (1)	1 (0)
102 - Relapsed or refractory disease within 12 months from initiating first-line chemoimmunotherapy	0 (0)	1 (1)	1 (0)
102 - Relapsed or refractory disease within 12 months of first-line chemoimmunotherapy	1 (1)	0 (0)	1 (0)
110 - Adequate renal, hepatic, pulmonary, cardiac function	5 (3)	7 (4)	12 (3)[a]
Missing data	20 (11)	10 (6)	30 (8)
803 - Missed 3 consecutive lab assessments from enrollment to Day 150	6 (3)	0 (0)	6 (2)
806 - Axicabtagene ciloleucel subjects: CRP results not available prior to conditioning chemotherapy	7 (4)	0 (0)	7 (2)
807 - Archived tumor tissue or fresh tumor tissue not collected prior to initiation of therapy	0 (0)	5 (3)	5 (1)
808 - Axicabtagene ciloleucel subjects: Day 50 antibody samples not collected	1 (1)	2 (1)	3 (1)
809 - Post randomization PET-CT not done for 2 or more consecutive time points, or 1 time point if followed by Progressive Disease	6 (3)	3 (2)	9 (3)
Due to COVID-19	3 (2)	1 (1)	4 (1)
SoC administration	0 (0)	3 (2)	3 (1)
401 - SoC therapy not administered per protocol	0 (0)	3 (2)	3 (1)

Data cutoff date = 18MAR2021.
Abbreviations: axicabtagene ciloleucel, axicabtagene ciloleucel; CLL, chronic lymphocytic leukemia; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IP, investigational product; IPD, important protocol deviations; PET-CT, positron emission tomography –computed tomography; PMBCL, primary mediastinal B-cell lymphoma; SoC, standard of care.
Notes: For subjects who received axicabtagene ciloleucel retreatment, only IPDs that occurred prior to the second conditioning chemotherapy infusion are summarized. Attribution to COVID-19 was included in the table only when the value was nonzero.
a Among the 12 subjects with IPD 110, 4 subjects (3 subjects with pulse oximetry not done and 1 subject with a neutrophil concentration of 0.99×10^3 cells/μL) were considered to be eligible by the clinical site.
Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 12

The Applicant's Position:

The deviations were not considered to impact the overall quality of the data and interpretation of the results.

The FDA's Assessment:
The protocol deviations that involved missed efficacy assessments were further analyzed given their clinical significance. Overall, 3% (6 subjects) of the subjects in the axicabtagene ciloleucel arm and 2% (3 subjects) of the subjects in the SOC arm missed PET-CT scan for 2 or more consecutive time points or 1 time point if followed by progressive disease.

Axicabtagene ciloleucel arm: Out of the six subjects, four subjects had imaging after missing two consecutive disease assessment indicating ongoing CR and therefore the missed assessments did not impact the overall efficacy assessment. The remaining 2 subjects were censored at the last evaluable disease assessment per the prespecified censoring rules outlined in the SAP.

SOC Arm: Out of the three subjects, one subject had event due to administration of NALT prior to missed imaging assessments. One subject missed a Day 100 assessment, however, Day 150 imaging revealed CR. This was followed by PD at an unscheduled assessment. Third subject missed several disease assessments after attaining a CR and was censored at the last evaluable disease assessment.

Reviewer's comment: The reviewer agrees that the missed efficacy assessments did not impact the interpretation of study results as more than half of these subjects had imaging after missed assessments that demonstrated ongoing CR. In addition, prespecified study rules for censoring were applied to both the arms in the remaining subjects.
The reviewer recommended that BIMO inspect the three clinical sites with the most IPDs.

Table of Demographic Characteristics

Data:

Demographic data for ZUMA-7 are summarized in
Table 9. Overall, subject demographics were generally comparable between the 2 treatment

arms. The median age was 59 years (range: 21 to 81 years), and 109 subjects (30%) were ≥ 65 years of age. The majority of subjects were male (237 subjects, 66%) and White (297 subjects, 83%).

Most subjects were randomized in North America (270 subjects, 75%), of whom the majority were in the US (250 subjects, 70%). Of the subjects randomized in Europe (79 subjects, 22%), most subjects were in the Netherlands (25 subjects, 7%).

Treatment arms were generally well balanced, but a difference of ≥ 10% was observed between the axicabtagene ciloleucel and SOCT arms for sex (male: 61% versus 71%, respectively).

Table 9. Applicant - ZUMA-7 Subject Demographics (FAS)

	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)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Other	10 (6)	8 (4)	18 (5)
Country, n (%)			
United States	130 (72)	120 (67)	250 (70)
Netherlands	11 (6)	14 (8)	25 (7)
Canada	10 (6)	10 (6)	20 (6)
Spain	6 (3)	9 (5)	15 (4)
United Kingdom	4 (2)	8 (4)	12 (3)
Belgium	4 (2)	3 (2)	7 (2)
France	4 (2)	2 (1)	6 (2)
Germany	1 (1)	5 (3)	6 (2)
Israel	4 (2)	2 (1)	6 (2)
Australia	2 (1)	2 (1)	4 (1)
Austria	1 (1)	2 (1)	3 (1)
Italy	2 (1)	1 (1)	3 (1)
Sweden	0 (0)	1 (1)	1 (0)
Switzerland	1 (1)	0 (0)	1 (0)
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)

Data cutoff date = 18MAR2021.
Abbreviations: FAS, full analysis set; Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; STDEV, standard deviation.
Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Table 10

The Applicant's Position:

Demographics of subjects in ZUMA-7 were generally representative of the r/r LBCL patient population. There were no noteworthy differences in demographics between the 2 treatment arms.

The FDA's Assessment:
The Agency agrees with the Applicant's demographic characteristics of the patient population.

It is noted that the median age of 59 years is younger than the median age of DLBCL patients (66 years) in the US reflecting the age of the study population that is transplant eligible. However, the median age of the study population is similar to the trials that have evaluated different chemoimmunotherapy regimens in transplant eligible R/R LBCL; for example, in the ORCHARRD trial, the median age was 57 years. Only 15% (53 subjects) of the enrolled population was ≥70 years of age indicating limited data in the older adults.

The male predominance noted in the study (66% males vs.34% females) may be explained by the overall male predominance in DLBCL.

While there is higher prevalence of DLBCL in the white compared to African American population, there is a disproportionate under-representation of the African American population (5%) in the study, although 70% of the study population was enrolled from the US.

Reviewer comment:
Overall, the study lacks racial diversity. In general, the two treatment arms are well balanced in terms of demographic characteristics. The 10% difference in the male subjects between the two arms is unlikely to impact the efficacy results given that subgroup analysis based on sex revealed treatment benefit in both genders.

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

Data:

Baseline characteristics for subjects in ZUMA-7 are summarized in Table 10.

Table 10. Applicant - ZUMA-7 Subject Demographics – Baseline Characteristics (FAS)

	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)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Response to first-line therapy at randomization (IxRS), n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤ 6 months of first-line therapy[a]	9 (5)	9 (5)	18 (5)
Relapse > 6 and ≤ 12 months of first-line therapy[a]	38 (21)	39 (22)	77 (21)
Second-line age-adjusted International Prognostic Index total score (IxRS), n (%)			
0 - 1	98 (54)	100 (56)	198 (55)
2 - 3	82 (46)	79 (44)	161 (45)
Derived response to first-line therapy at randomization, n (%)			
Primary refractory	133 (74)	132 (74)	265 (74)
Relapse ≤ 6 months of the completion of the first-line therapy[a]	26 (14)	22 (12)	48 (13)
Relapse > 6 and ≤ 12 months of the completion of the first-line therapy[a]	20 (11)	24 (13)	44 (12)
Missing	1 (1)	1 (1)	2 (1)
Derived second-line age-adjusted International Prognostic Index total score, n (%)			
0	26 (14)	18 (10)	44 (12)
1	68 (38)	82 (46)	150 (42)
2	86 (48)	79 (44)	165 (46)
0 or 1	94 (52)	100 (56)	194 (54)
2 or 3	86 (48)	79 (44)	165 (46)
Second-line age-adjusted International Prognostic Index (investigator), n (%)			
ECOG performance status > 1	0 (0)	0 (0)	0 (0)
Stage III/IV	139 (77)	146 (82)	285 (79)
Elevated LDH (LDH > ULN per local laboratory reference range)	101 (56)	94 (53)	195 (54)
Disease type per investigator, 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)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Large cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)
HGBL with or without MYC and BCL2 and/or BCL6 rearrangement	43 (24)	27 (15)	70 (19)
Primary cutaneous DLBCL (leg type)	1 (1)	0 (0)	1 (0)
Other	0 (0)	3 (2)	3 (1)
Molecular subgroup per investigator, n (%)			
GCB-like	96 (53)	84 (47)	180 (50)
Non-GCB-like	47 (26)	54 (30)	101 (28)
Not tested	37 (21)	41 (23)	78 (22)
Double expressor lymphoma as determined per investigator, n (%)			
Yes	44 (24)	35 (20)	79 (22)
No	85 (47)	93 (52)	178 (50)
Not tested	51 (28)	51 (28)	102 (28)
Double-/triple-hit status per investigator, n (%)			
HGBL – double-hit	30 (17)	18 (10)	48 (13)
HGBL - triple-hit	10 (6)	16 (9)	26 (7)
Negative	110 (61)	102 (57)	212 (59)
Not tested	30 (17)	43 (24)	73 (20)
Disease stage, n (%)			
I	10 (6)	6 (3)	16 (4)
II	31 (17)	27 (15)	58 (16)
III	35 (19)	33 (18)	68 (19)
IV	104 (58)	113 (63)	217 (60)
Molecular subgroup per central laboratory, n (%)[b]			
GCB-like	109 (61)	99 (55)	208 (58)
ABC-like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing	28 (16)	41 (23)	69 (19)
Disease type per central laboratory, n (%)			
DLBCL NOS/without further classification possible[c]	126 (70)	120 (67)	246 (69)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
HGBL, NOS	0 (0)	1 (1)	1 (0)
HGBL, with MYC/BCL2/BCL6 Rearrangements	31 (17)	25 (14)	56 (16)
Not Confirmed	15 (8)	13 (7)	28 (8)
Other	5 (3)	5 (3)	10 (3)
Missing	3 (2)	15 (8)	18 (5)
Prognostic marker per central laboratory, n (%)			
HGBL – double-hit	25 (14)	15 (8)	40 (11)
HGBL – triple-hit	6 (3)	10 (6)	16 (4)
Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
NA[d]	74 (41)	70 (39)	144 (40)
Missing	3 (2)	15 (8)	18 (5)
CD19 IHC positive by central laboratory at baseline, n (%)[e]			
Yes	144 (80)	134 (75)	278 (77)
No	13 (7)	12 (7)	25 (7)
Missing	23 (13)	33 (18)	56 (16)
CD19 H-Score, n (%)			
≤ 150	85 (47)	67 (37)	152 (42)
> 150	72 (40)	79 (44)	151 (42)
Missing[f]	23 (13)	33 (18)	56 (16)
Presence of B symptoms, n (%)			
Yes	21 (12)	29 (16)	50 (14)
No	159 (88)	150 (84)	309 (86)
S (Splenic involvement), n (%)			
Yes	19 (11)	33 (18)	52 (14)
No	161 (89)	146 (82)	307 (86)
E (Extranodal disease), n (%)			
Yes	103 (57)	120 (67)	223 (62)
No	77 (43)	59 (33)	136 (38)
X (Bulky disease), n (%)			
Yes	13 (7)	16 (9)	29 (8)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
No	167 (93)	163 (91)	330 (92)
Bone marrow involvement[g], n (%)			
Yes	17 (9)	15 (8)	32 (9)
No	163 (91)	164 (92)	327 (91)
Screening bone marrow assessment[h], n (%)			
Lymphoma present	17 (9)	14 (8)	31 (9)
If PET/CT, result			
Focal involvement	5 (3)	9 (5)	14 (4)
Diffuse involvement	8 (4)	1 (1)	9 (3)
Lymphoma not present	161 (89)	164 (92)	325 (91)
If PET/CT, result			
Negative	126 (70)	127 (71)	253 (70)
Focal involvement[i]	1 (1)	0 (0)	1 (0)
Diffuse involvement[i]	1 (1)	0 (0)	1 (0)
Indeterminate	0 (0)	1 (1)	1 (0)
If PET/CT, result			
Bone marrow not evaluable	0 (0)	1 (1)	1 (0)
Number of prior lines of therapy, n (%)			
1	180 (100)	179 (100)	359 (100)

Data cutoff date = 18MAR2021.

Abbreviations: ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; GCB, germinal center B-cell; HGBL, high-grade B-cell lymphoma; IHC, immunohistochemistry; IxRS, interactive voice/web response system; LDH, lactate dehydrogenase; Max, maximum; Min, minimum; NA, not applicable; NOS, not otherwise specified; PET/CT, positron emission tomography-computed tomography; Q1, first quartile; Q3, third quartile; STDEV, standard deviation; ULN, upper limit of normal.

Notes: One subject did not perform screening bone marrow assessment; another subject's screening bone marrow assessment was not evaluable. One subject signed the wrong informed consent form and then signed the correct one after randomization. HGBL – double-hit is defined as presence of *MYC* and either *BCL-2* or *BCL6* rearrangements; HGBL – triple-hit is defined as presence of *BCL-2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of *MYC* and *BCL-2* proteins not related to underlying chromosomal rearrangements.

a For data collected in the IxRS, relapse after first-line therapy was assessed for subjects enrolled until Amendment 4 using ≤ 6 months from initiation of first-line therapy and using ≤ 6 months of first-line therapy for subjects enrolled after Amendment 4; this also applies for relapse > 6 months ≤ 12 months. Data derived from the clinical database assessed relapse after first-line therapy using ≤ 6 months of completion of first-line therapy.

b Missing records of molecular subgroup per central laboratory are due to insufficient tissue or biopsy not available at central laboratory. NA in the molecular subgroup per central laboratory category indicates the sample failed to meet quality control.

c Disease type was considered to be DLBCL, NOS, when all other disease subtypes could be excluded by laboratory analyses; cases of incomplete evaluation (eg, inadequate samples or sample types) were considered to be DLBCL without further classification of subtype possible. Per the central laboratory, DLBCL NOS = 32 subjects (18%) and 26 subjects (15%) in the

axicabtagene ciloleucel and SOCT arms, respectively; and DLBCL without further classification possible = 94 subjects (52%) and 94 subjects (53%), respectively.

d Disease types (per central laboratory) of DLBCL, NOS; HGBL, NOS; other; and not confirmed are assigned "NA" in prognostic marker per central laboratory.

e CD19 IHC positive is defined as the H-score of staining greater than or equal to 5.

f Missing CD19 H-scores are mainly due to quantity not sufficient, biopsy not available at central laboratory, CD19 negative, or tumor tissue not present in sample.

g Bone marrow involvement is collected on the diagnosis history case report form.

h Screening bone marrow assessment is done by aspirate and biopsy or PET/CT.

i In these cases, reports of focal or diffuse involvement indicates fluorodeoxglucose uptake but may not indicate lymphoma involvement per investigator discretion.

Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 11

The Applicant's Position:

There were no noteworthy differences in demographics between the 2 treatment arms. Baseline characteristics were generally comparable with the overall r/r LBCL subject population. Overall, ZUMA-7 included a high percentage of subjects with known high-risk features that are associated with a poor prognosis.

The FDA's Assessment:

1. The two arms are balanced in the number of subjects with primary refractory versus relapsed lymphoma and low versus high second- line age-adjusted IPI total score.
2. It is noted that 74% of subjects randomized in the study had primary refractory disease (did not attain CR with first-line chemoimmunotherapy) and 26% of the subjects relapsed within 1 year of first-line therapy. Out of the 93 subjects that had best response of CR to front-line therapy, 79 subjects (85%) had relapse within 12 months of initiating first-line therapy. Thirteen subjects (14%) had relapse > 12 months after initiating first- line therapy and within 12 months of completing first- line therapy. One subject (b) (6) did not relapse from first line therapy. This subject was noted to have a false positive PET-CT (no biopsy confirmation) and remained in remission without subsequent therapy.
3. Twenty four percent of subjects in the axicabtagene ciloleucel arm had high grade B-cell lymphoma with or without MYC and BCL2 and/or BCL 6 rearrangement as opposed to 15% in the SOC arm. Given that high grade B- cell lymphoma in r/r setting may be associated with a worse outcome compared to other histological subgroups of LBCL, this difference is unlikely to skew efficacy in favor of axicabtagene ciloleucel arm.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance:

Of the 180 subjects randomized to the axicabtagene ciloleucel arm, 178 (99%) underwent leukapheresis, of whom 172 (96%) received lymphodepleting chemotherapy, and 170 (94%) received and completed axicabtagene ciloleucel treatment (Safety Analysis Set [SAS]). The median weight-adjusted dose administered to subjects who weighed ≤ 100 kg (137 subjects) was 2.0×10^6 anti-CD19 CAR T cells/kg (range: 1.0 to 2.1×10^6 anti-CD19 CAR T cells/kg). The

33 subjects who weighed > 100 kg all received the planned flat dose of 2×10^8 anti-CD19 CAR T cells/kg. In the axicabtagene ciloleucel arm of the SAS, the planned total body surface area (BSA)-adjusted dose (± 10%) of cyclophosphamide (1,500 mg/m^2) and fludarabine (90 mg/m^2) was administered to 165 subjects and 164 subjects, respectively, of the 169 subjects with available BSA-adjusted dose information. Overall, 166 subjects (98%) received within 10% of the planned dose of axicabtagene ciloleucel.

For the 168 subjects in the SOCT arm of the SAS, 152 subjects (90%) received 2 or 3 cycles as directed by the protocol, and 16 subjects (10%) received 1 cycle of salvage chemotherapy. Among the subjects who received 2 or 3 cycles of salvage chemotherapy and had a CR or PR, 62 subjects (37% of the SOCT - SAS) went on to receive HDT auto-SCT and 3 subjects (2% of the SOCT - SAS), excluding disease progression or those who initiated HDT but did not complete auto-SCT, did not (1 subject was considered to have an insufficient response by the investigator, 1 subject had a PR prior to Study Day 50 and PD at Study Day 50, and 1 subject had a TEAE of blood stem cell harvest failure).

Of the 179 subjects in the FAS randomized to the SOCT arm, 168 (94%) received at least 1 dose of salvage chemotherapy. The majority of subjects in the SOCT arm (152 subjects [85%]) received at least 2 cycles of salvage chemotherapy. Of subjects who responded to salvage chemotherapy, 64 subjects (36% of the FAS) received HDT and reached HDT-auto-SCT, of whom 62 (received CD34$^+$ stem cell rescue (auto-SCT) on protocol and 2 received CD34$^+$ stem cell rescue off protocol.

The FDA's Assessment:
Axicabtagene ciloleucel Arm: Out of 170 subjects treated with axicabtagene ciloleucel**,** 33 subjects weighed more than 100 kg and all of these subjects received 200 x10e8 CAR+ T cells. For the 137 subjects that weighed ≤100 kg, the median weight adjusted dose for this subgroup was 2x10e6 CAR+T cells/kg with range of 1.0-2.1x10e6cells/kg. Within this subgroup, four subjects received <2 x10e6CAR+T cells/kg (Range:1.0-1.6 x10e6 CAR+T cells/kg) and seven subjects received 2.1x10e6 CAR+T cells/kg.

Reviewer comment:
Given the ITT nature of efficacy analysis, all patients are included in the efficacy analysis regardless of the dose that was administered. The dosing variability in a small number of subjects is unlikely to impact the efficacy analysis. Two subjects treated with the non-conforming product are included in the efficacy analysis but excluded from safety analysis.

SOC Arm: Out of the 168 subjects that received any salvage chemoimmunotherapy, 16 subjects (9%) received only one cycle of chemotherapy. None of these subjects attained a response per investigator or IRC and none proceeded to high dose therapy with autologous stem cell transplantation. The remaining 152 subjects (85%), received two to three cycles of chemotherapy (91 subjects received two cycles and 61 subjects received three cycles of chemotherapy). Out of the 168 subjects, 50% (84 subjects) received R-ICE, 25% (42 subjects) received R-GDP, 22% (37 subjects) received R-DHAP/R-DHAX and 3% (5 subjects) received R-ESHAP.

Concomitant Medications and Rescue Medication Use:

Among subjects who received axicabtagene ciloleucel, 77 subjects (45%) received corticosteroids (with or without tocilizumab), 112 subjects (66%) received tocilizumab (with or without corticosteroids), 68 subjects (40%) received corticosteroids and tocilizumab, and 28 subjects (16%) were treated with immunoglobulins. Nineteen (11%) subjects were treated with vasopressors. (m5.3.5.1, ZUMA-7 Primary Analysis CSR Section 11.9).

The Applicant's Position:
No treatment compliance issues were identified. AEs of interest such as CRS and neurologic events were mostly reversible and manageable with medical interventions and supportive care. Forty-one subjects received systemic steroids for the management of CRS, 55 subjects received corticosteroids for the management of neurotoxicity. 33 subjects received steroids for the management of "other" AEs.
In addition, 4 subjects received steroids for medical history, 32 subjects received steroids for prophylaxis and 14 subjects received steroids for "other" indication.

The FDA's Assessment:
Since the safety profile and the concomitant medication use of the SOC arm is well characterized, this section will discuss the concomitant medication use for the safety population in the axicabtagene ciloleucel arm.

The Applicant defines concomitant medications of interest as medications that were administered in the period from initiation of axicabtagene ciloleucel infusion through hospital discharge except immunoglobulins which are included if administered on or after the first axicabtagene ciloleucel infusion. FDA does not agree with this definition and considers medications of interest as concomitant regardless of whether they were administered prior to or after hospital discharge post-treatment. FDA analysis of concomitant medications is based on the safety population (n=168) and excludes the two subjects that received non-conforming product.

Axicabtagene ciloleucel arm:
Tocilizumab:
Based on the ADCM dataset, total of 112 (67%) subjects were treated with tocilizumab (with or without steroids).

111 (66%) subjects received tocilizumab for the management of CRS; 25 subjects (15%) received tocilizumab for the management of neurotoxicity (NT), out of which only one subject (b) (6) received tocilizumab only for the management of neurotoxicity. The remaining 24 subjects received tocilizumab for the management of both CRS and neurotoxicity either within the same administration or other administrations.

Corticosteroids:
Based on ADCM dataset, total of 92 subjects (55%) received systemic corticosteroids (with or

without tocilizumab). Steroids were administered to 58 subjects (35%) for the management of NT and 41 subjects (24%) for the management of CRS, and 78 subjects (46%) received both tocilizumab and steroids. Four subjects received steroids for underlying medical history and 24 subjects received steroids for management of other adverse events.

Immunoglobulins:
27 subjects (16%) were treated with immunoglobulins.

Vasopressors:
16 subjects (9.5%) received systemic vasopressors.

Nonsteroidal Immunosuppressants:
Four subjects (2%) received nonsteroidal immunosuppressive agents other than tocilizumab: Anakinra, siltuximab and tacrolimus. One subject received anakinra for the management of neurotoxicity and one subject received siltuximab for the management of CRS/NT with suboptimal response to steroids. One subject received anakinra for the management of COVID-19 infection. One subject received tacrolimus for the treatment of autoimmune neutropenia.

Table 11. FDA - Concomitant Medications of Interest in Axicabtagene Ciloleucel Arm

Medication Class	**N=168 (%)**
Tocilizumab used to manage CRS Tocilizumab used to manage NT	111 (66%) 25 (15%)
Systemic steroids used to manage CRS Systemic steroids used to manage NT	41 (24%) 58 (35%)
Tocilizumab and steroids to manage CRS Steroids and tocilizumab to manage NT	38 (23%) 18 (11%)
Steroids or tocilizumab to manage CRS Steroids or tocilizumab to manage NT	114 (68%) 65 (39%)
Vasopressors used to manage CRS	12 (7%)

Source: FDA analysis of ADCM dataset and Applicant IR dated 2/24/2022

Reviewer comment:
1. According to the ADCM dataset , 11 subjects received tocilizumab for the management of " other" indication. To ensure that "other" indication did not include subjects that were treated for symptoms indicative of CRS and not flagged as CRS , these events were further analyzed. Four subjects were administered tocilizumab for management of events that FDA adjudicated as neurotoxicity events. Five additional subjects received tocilizumab for management of symptoms that the review team considered as manifestation of CRS. Two subjects received tocilizumab both for management of CRS and overlapping symptoms of tachycardia due to

neutropenic fever and hypotension due to sepsis respectively. No additional cases of CRS were identified. For additional details, please see Section 8.2.5: CRS and Neurotoxicity.

Subsequent therapies:
This section refers to the FAS population. Out of the 179 subjects in the SOC arm (FAS), 71% received any subsequent therapy; 55% received autologous CD19-directed CAR T therapy, 40% received chemoimmunotherapy, 22% received other therapies (not including anti-CD20), 16% received antibody drug conjugates (polatuzumab +/-BR), 15% received radiation therapy alone, 10% received immunomodulatory agents and 4% received autologous stem cell therapy.

Out of 180 subjects in the axicabtagene ciloleucel arm (FAS), 47% received any subsequent therapy. 38% received chemoimmunotherapy, 22% received other therapies (not including anti-CD20), 14% received antibody drug conjugates (polatuzumab +/-BR), 8% received radiation therapy alone, 7% received immunomodulatory agents and 7% received autologous stem cell transplant.

Reviewer comment: The lower use of subsequent therapy in the axicabtagene ciloleucel arm compared to the SOC arm is reflective of the higher efficacy of axicabtagene ciloleucel. While cross-over was not built into the study design, 55% of subjects in the SOC arm received autologous CD19-directed CAR T therapy which may confound difference in OS between the two arms. It is noted that none of the subjects in the axicabtagene ciloleucel arm underwent HSCT while in response.

Data Quality and Integrity

The Applicant's Position:

All data were collected via an electronic case report form (eCRF) system, and source document verification of CRF data was performed at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations was confirmed. Investigators assured cooperation and compliance with the monitoring visits. Site audits were to include an inspection of the facility(ies), review of subject and study-related records, and compliance with protocol requirements, ICH/GCP, and applicable regulatory policies. Additional information is provided in m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 7.6.

The FDA's Assessment:
FDA requested that the Applicant submit new datasets that reflect FDA's adjudication of CRS and neurotoxicity. The Applicant submitted the updated datasets ADAEFDA, ADCRSFDA, ADNEFDA, ADSAFFDA and ADCRSNTFDA under 125643/398/14 on 1/26/2022 e seq 431. Dataset ADSAFFDA was updated by the Applicant and resubmitted on 3 February 2021 under 125634/394/18 eSeq 437 to include a flag to identify FDA adjudicated NT events. An updated ADAEFDA dataset was submitted on 7 February 2022 under 125643/394/21 which included flags AELK01FL and AECC01FL to identify the AEs that occurred in the leukapheresis and conditioning chemotherapy period. Updated ADLBFDA dataset were submitted on February 22,

2022 under 125643/394/25 e seq 447 using FDA's definition of baseline labs and additional flags to identify lab-shift analysis. Updated integrated ADLB datasets (ZUMA-1, ZUMA-5 and ZUMA-7) were submitted on March 7, 2022 under 125643/394/28 e seq 453. FDA's adjudicated datasets were used for all safety analyses. The originally submitted datasets were used for efficacy analysis.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)
Data:

The primary efficacy endpoint was EFS with progression events and censoring per blinded central assessment. EFS was defined as the time from randomization to the earliest date of disease progression per the Lugano Classification {Cheson 2014} per blinded central review, commencement of new lymphoma therapy, or death from any cause. EFS is an established time to-event endpoint and is correlated with OS in DLBCL {Maurer 2014}. The hypothesis was that axicabtagene ciloleucel will prolong EFS compared with SOCT in adult subjects with r/r LBCL. The hypothesized treatment effect corresponds to a 50% improvement in the median EFS.

At the time of the data cutoff (18 March 2021), a total of 252 EFS events occurred as per blinded central assessment, 108 in the axicabtagene ciloleucel arm and 144 in the SOCT arm. ZUMA-7 demonstrated that axicabtagene ciloleucel was superior to SOCT as measured by EFS with a stratified HR of 0.398 (95% CI: 0.308, 0.514) and log-rank p-value of < 0.0001 (Table 12 and Figure 5).

The Kaplan-Meier (KM) median EFS time was longer in the axicabtagene ciloleucel arm (8.3 months [95% CI: 4.5, 15.8]) than in the SOCT arm (2.0 months [95% CI: 1.6, 2.8]).

At the time of the data cutoff, the KM estimate of the percentage of subjects who remained event free at Month 12 was 47.2% and 17.6% in the axicabtagene ciloleucel arm and SOCT arm, respectively, and 40.5% and 16.3%, respectively, at Month 24.

Table 12. Applicant - EFS per Blinded Central Assessment (FAS)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Number of subjects	180	179
Events, n (%)	108 (60)	144 (80)
Censored[a], n (%)	72 (40)	35 (20)
Stratified log-rank p-value	<0.0001	NA
Hazard ratio (95% CI), stratified	0.398 (0.308, 0.514)	NA
Stratified (derived) log-rank p-value	<0.0001	NA
Hazard ratio (95% CI), stratified (derived)	0.406 (0.313, 0.525)	NA

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Unstratified log-rank p-value	<0.0001	NA
Hazard ratio (95% CI), unstratified	0.423 (0.328, 0.544)	NA
KM median (95% CI) EFS time (months)	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
Min, Max EFS time (months)	0, 31+	0+, 33+
Event		
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[b], 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) by KME		
6 month	51.1 (43.6, 58.1)	26.6 (20.2, 33.3)
12 month	47.2 (39.8, 54.3)	17.6 (12.3, 23.6)
24 month	40.5 (33.2, 47.7)	16.3 (11.1, 22.2)
Median (95% CI) follow-up time (months) (reverse KM approach)	23.0 (20.9, 24.0)	21.2 (20.4, 23.7)

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; EFS, event-free survival; FAS, Full Analysis Set; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; SCT, stem cell transplant; SD, stable disease.

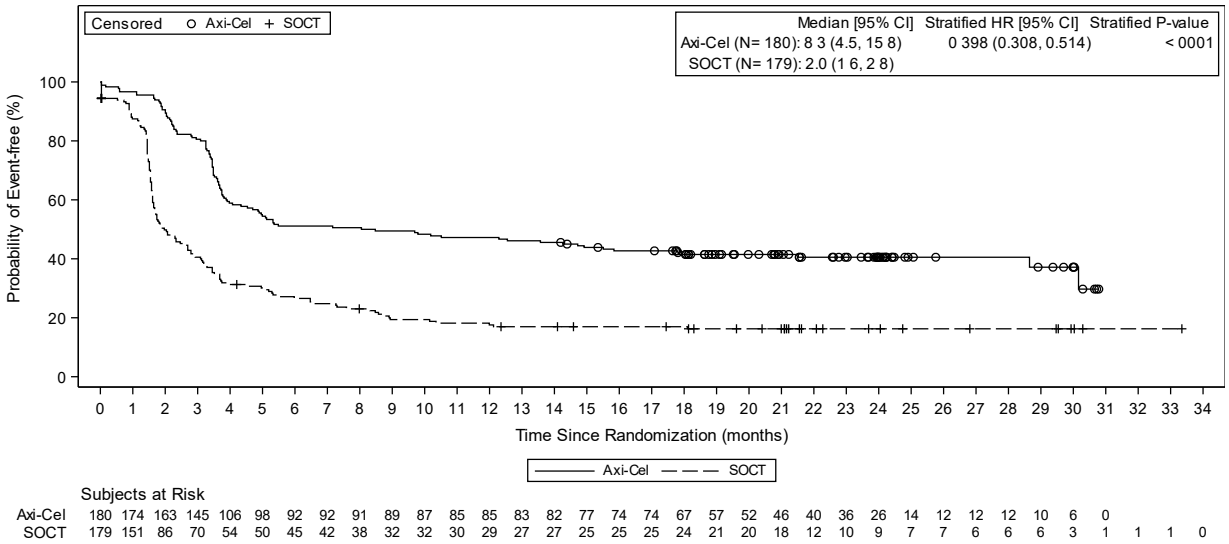
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. The derived stratification factors are based on data collected on case report forms. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95%

CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

a. Only 8 subjects (all in the standard of care therapy arm) of a total of 359 subjects were censored before Month 12 (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listing 16.2.1.1).
b. A total of 12 subjects (2 in the axicabtagene ciloleucel arm and 10 in the standard of care therapy arm) initiated a new lymphoma therapy in the absence of any post-baseline evaluable disease assessment (m5.3.5.1, ZUMA-7 Primary Analysis CSR, Listings 16.2.1.1 and 16.2.1.2) and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

Source: m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 11.

Figure 5. Applicant - KM Plot of EFS per Blinded Central Assessment (FAS)



Data cutoff date = 18MAR2021.

Abbreviations: Axicabtagene ciloleucel, axicabtagene ciloleucel; CI, confidence interval; EFS, event-free survival; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; SCT, stem cell transplant; SOCT, standard of care therapy.

Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause.

The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system.

Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. The Breslow method is used to handle the ties for the Cox regression models.

One-sided p-value from log rank test is presented. Event/Censoring time was calculated as Event/Censoring date – Randomization date +1 (= days) / 30.4375 (= months). Of note, only 8 subjects (all in the SOCT arm) of a total of 359 subjects were censored before Month 12 (m5.3.5.1, ZUMA 7 Primary Analysis CSR, Listing 16.2.1.1). A total of 12 subjects (2 in the axicabtagene ciloleucel arm and 10 in the SOCT arm) initiated a new lymphoma therapy in the absence of any post-baseline evaluable disease assessment (m5.3.5.1, ZUMA 7 Primary Analysis CSR, Listings 16.2.1.1 and 16.2.1.2) and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Figure 4

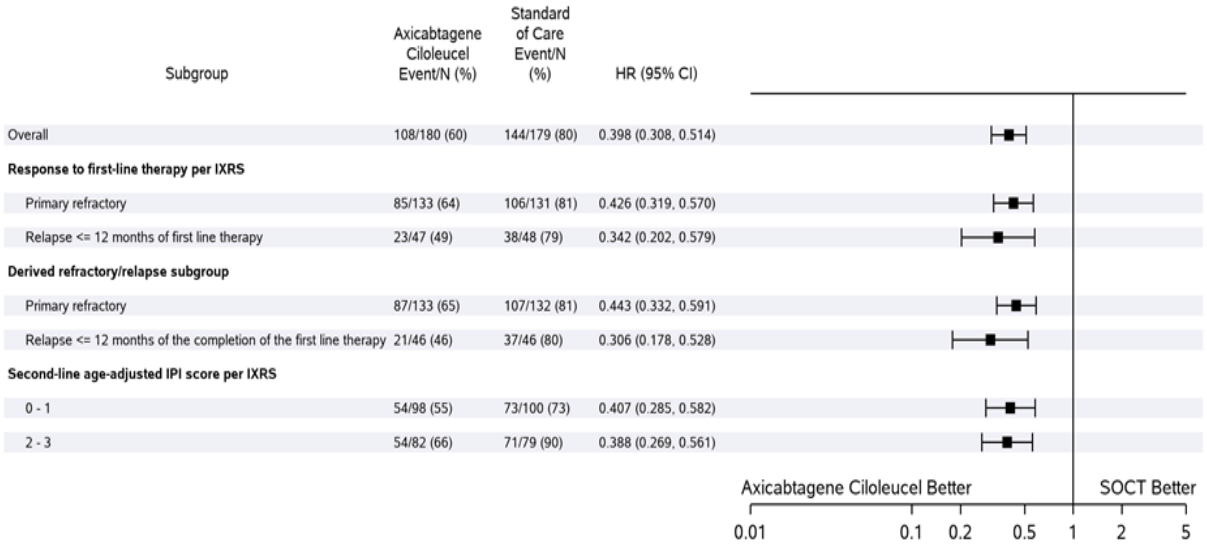
The primary analysis of EFS used the stratification factors as collected via the Interactive Voice/Web (x) Response System at randomization. Sensitivity analyses of EFS using stratification factors derived from the eCRF and EFS without stratification also demonstrated axicabtagene ciloleucel superiority (stratified [derived] HR of 0.406 [95% CI: 0.313, 0.525],

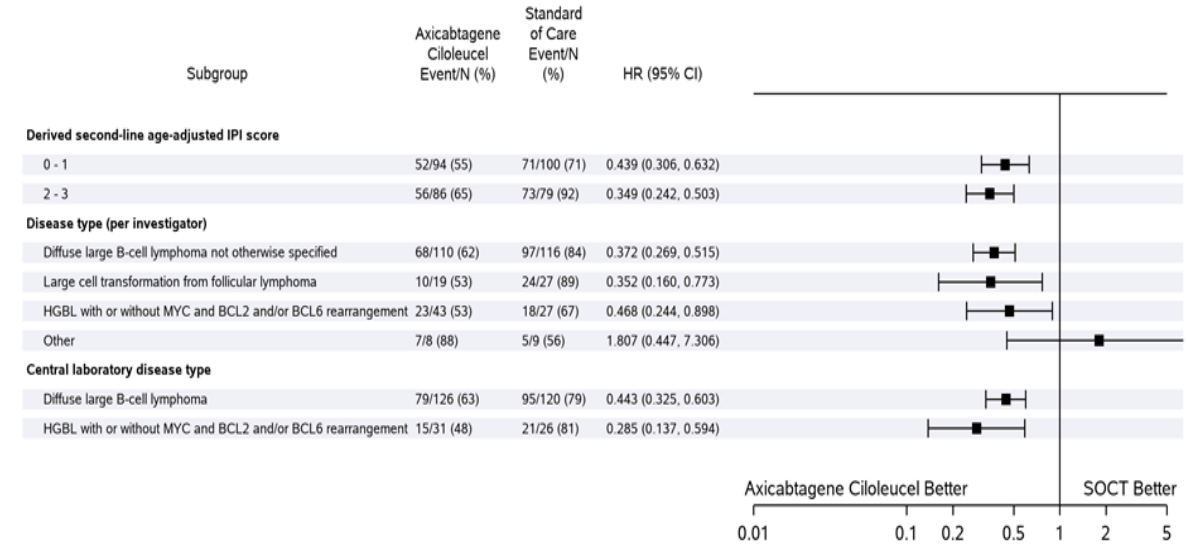
log-rank p < 0.0001; unstratified HR of 0.423 [95% CI: 0.328, 0.544], log-rank p < 0.0001, respectively).

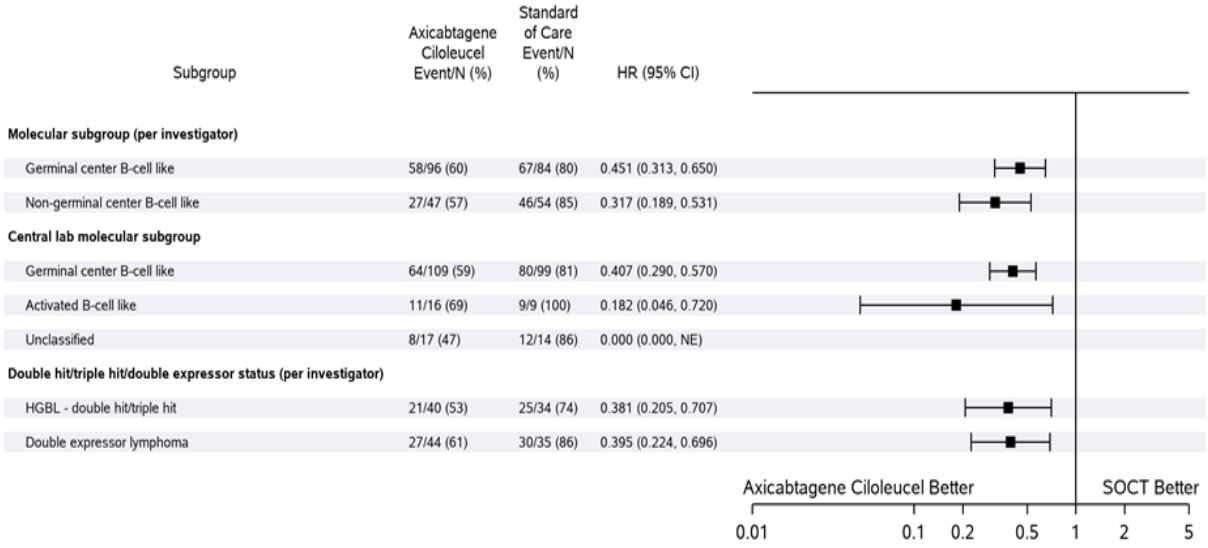
EFS per investigator assessment and prespecified sensitivity analyses were consistent with the primary EFS analysis.

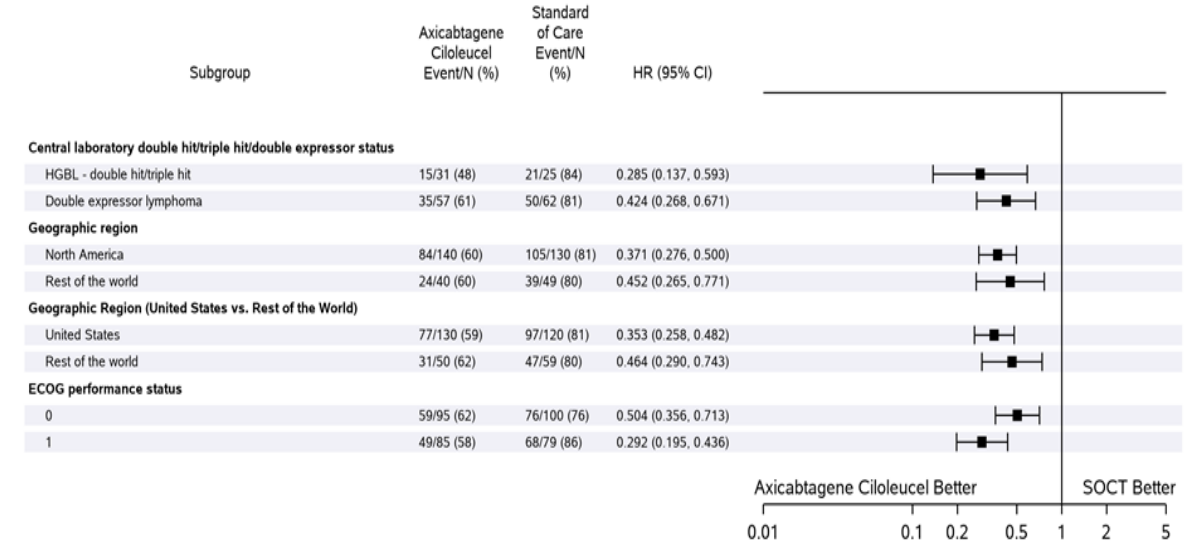
Subgroup analysis of EFS were performed based on baseline demographic and disease characteristics. Across the majority of subgroups, HRs favored axicabtagene ciloleucel over SOCT (Figure 6). Data should be interpreted with caution for subgroups that included few subjects.

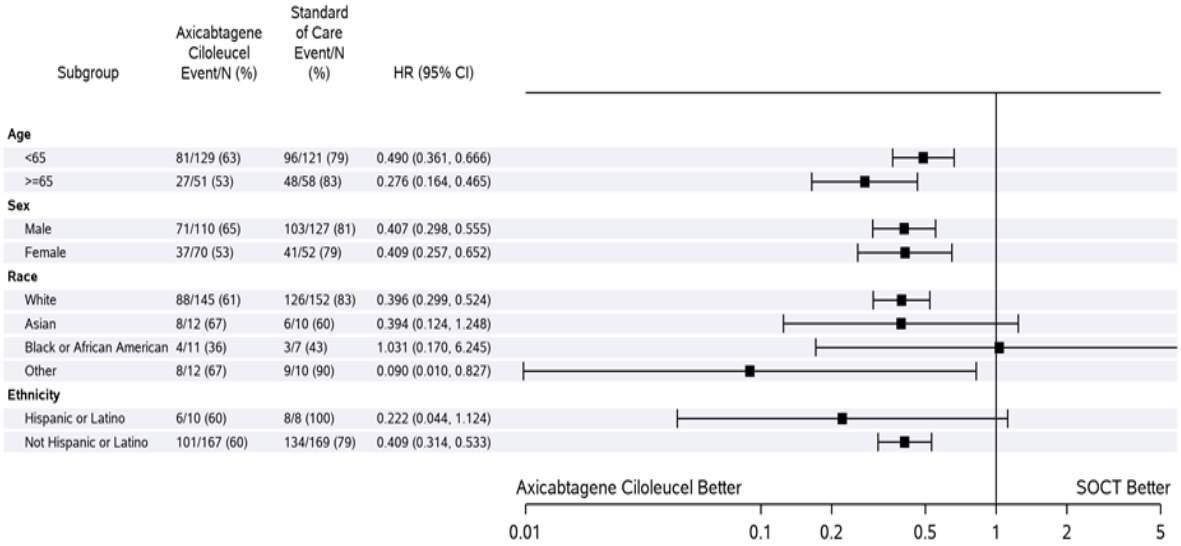
Figure 6. Applicant – Forest Plot of EFS by Subgroups per Central Assessment (FAS)






Subgroup
Axicabtagene Ciloleucel Event/N (%)
Standard of Care Event/N (%)
HR (95% CI)
Molecular subgroup (per investigator)
Germinal center B-cell like 58/96 (60) 67/84 (80) 0.451 (0.313, 0.650)
Non-germinal center B-cell like 27/47 (57) 46/54 (85) 0.317 (0.189, 0.531)
Central lab molecular subgroup
Germinal center B-cell like 64/109 (59) 80/99 (81) 0.407 (0.290, 0.570)
Activated B-cell like 11/16 (69) 9/9 (100) 0.182 (0.046, 0.720)
Unclassified 8/17 (47) 12/14 (86) 0.000 (0.000, NE)
Double hit/triple hit/double expressor status (per investigator)
HGBL - double hit/triple hit 21/40 (53) 25/34 (74) 0.381 (0.205, 0.707)
Double expressor lymphoma 27/44 (61) 30/35 (86) 0.395 (0.224, 0.696)
Axicabtagene Ciloleucel Better
SOCT Better
0.01
0.1
0.2
0.5
1
2
5


Subgroup
Axicabtagene Ciloleucel Event/N (%)
Standard of Care Event/N (%)
HR (95% CI)
Central laboratory double hit/triple hit/double expressor status
HGBL - double hit/triple hit 15/31 (48) 21/25 (84) 0.285 (0.137, 0.593)
Double expressor lymphoma 35/57 (61) 50/62 (81) 0.424 (0.268, 0.671)
Geographic region
North America 84/140 (60) 105/130 (81) 0.371 (0.276, 0.500)
Rest of the world 24/40 (60) 39/49 (80) 0.452 (0.265, 0.771)
Geographic Region (United States vs. Rest of the World)
United States 77/130 (59) 97/120 (81) 0.353 (0.258, 0.482)
Rest of the world 31/50 (62) 47/59 (80) 0.464 (0.290, 0.743)
ECOG performance status
0 59/95 (62) 76/100 (76) 0.504 (0.356, 0.713)
1 49/85 (58) 68/79 (86) 0.292 (0.195, 0.436)
Axicabtagene Ciloleucel Better
SOCT Better
0.01
0.1
0.2
0.5
1
2
5



Data cutoff date = 18MAR2021
Abbreviations: BCL, B-cell lymphoma; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HGBL, high-grade B-cell lymphoma; HR, hazard ratio; IPI, International Prognostic Index; IxRS, interactive voice/web response system; NE, not estimable; SOCT, standard of care therapy.
Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy (including stem cell transplant in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and/or second-line age-adjusted IPI (0 to 1 versus 2 to 3) as collected via IxRS. Stratified Cox regression models are used to provide the estimated HR and 2-sided 95% CIs for axicabtagene ciloleucel relative to SOCT. The Breslow method is used to handle the ties for the Cox regression models. Disease type of "Other" includes T-cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus+ DLBCL, primary cutaneous DLBCL (leg type), and other types. HGBL – double-hit is defined as presence of *MYC* and either *BCL2* or *BCL6* rearrangements; HGBL – triple-hit is defined as presence of *BCL2*, *BCL6*, and *MYC* rearrangements; double-expressor lymphoma is defined as overexpression of MYC and BCL2 proteins not related to underlying chromosomal rearrangements. In the central laboratory molecular unclassified subgroup, the number of subjects and/or number of events are sparse across stratification factors between the treatment arms and resulted in an estimated HR < 0.00001.
Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Figure 5.

The Applicant's Position:

The primary objective of ZUMA-7 was met: axicabtagene ciloleucel treatment resulted in a statistically significant reduction in the risk of an EFS event compared with SOCT (stratified HR = 0.398 [95% CI: 0.308, 0.514]; stratified log-rank p < 0.0001).

These data should be viewed in the context of the study populations of historical studies. The ZUMA-7 population consisted of subjects who were either refractory to first-line therapy or relapsed within 12 months of first-line therapy. In comparison, published studies of second-line SOCT in patients with r/r DLBCL included approximately 29% of patients with disease that relapsed > 12 months after first-line therapy (ORCHARRD study {van Imhoff 2017a}) or approximately 54% of patients who relapsed > 12 months after diagnosis (Collaborative Trial in Relapsed Aggressive Lymphoma [CORAL] study {Gisselbrecht 2010}). However, when comparing the outcomes for the ZUMA-7 SOCT arm with comparable subpopulations in historical studies, particularly those who had received prior rituximab or had primary refractory or relapsed

disease within 12 months of first-line therapy, the outcomes of EFS for SOCT were comparable to the ORCHARRD and CORAL studies. The 2 year EFS rate for the SOCT arm in ZUMA 7 (16.3%) is similar to the 2-year EFS rate in the ORCHARRD study (18%) {van Imhoff 2017b}, in which all subjects had received prior rituximab and included 71% of patients with primary refractory and relapsed disease within 12 months. The ZUMA-7 SOCT arm 2-year EFS rate is also similar to the 2-year EFS rate (approximately 16%) for the subgroup of patients in the CORAL study whose disease was refractory or relapsed < 12 months from diagnosis and whose previous therapy included rituximab. In comparison, the 2-year EFS rate for the axicabtagene ciloleucel arm of ZUMA 7 was 40.5%.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the outcome of the SOC arm was as expected when reviewed in context with the historical data from the CORAL and ORCHARRD studies. Given the limitation of cross-trial comparison, the ORR, CR rate, 2-year EFS and PFS rate are comparable across ZUMA-7 SOC arm and historical data indicating that the SOC arm did not underperform in ZUMA 7. (Refer to Table 2 under FDA assessment in Section 2.2).

Table 13. FDA - Events in ZUMA-7

Event Category per Central Assessment	Axicabtagene ciloleucel Arm N=180	SOC Arm N= 179
Death without documented prior event	11	3
Disease progression at planned disease assessment prior to NALT(inc. ReRx) or HSCT	68	40
Disease progression in b/w planned disease assessments prior to NALT(inc. ReRx) or HSCT	14	17
Disease progression or death after HSCT Death PD	NA	21 03 18
Subjects with SD by Day 150	4	0
Subjects with CR or PR and subsequently received NALT wo disease progression	8	24
Subjects with SD and received NALT without disease progression	1	29
NALT in the absence of any evaluable disease assessment	2	10
Total Events	108	144

- NALT includes retreatment in two subjects in the axicabtagene ciloleucel arm
- Source: FDA analysis of ADTTE dataset

A higher number of EFS events in the SOC arm compared to axicabtagene ciloleucel arm were

due to administration of NALT (35% vs. 6%) as opposed to PD or death. Since the treating investigators' decision to administer NALT could be potentially subject to bias given the open label nature of the study, we further analyzed subjects that received NALT constituting EFS events.

1. Subjects with CR or PR and subsequently received NALT without disease progression:
SOC arm:
24 subjects in the SOC arm (13%) received NALT while in CR or PR in the absence of disease progression per central review. This included 19 subjects that investigators either considered as non-responders or as having disease progression (after attaining a response) prompting NALT which constituted an event, when in-fact these subjects were ongoing responders per central review: Per investigator assessment, fourteen subjects were determined to be non-responders and therefore were not eligible to proceed to HSCT, two subjects responded but subsequently progressed of which one subject received off protocol NALT and another subject received off protocol HSCT. Three subjects responded ,underwent HSCT and were then determined to have disease progression prompting administration of NALT.

One additional subject was inadvertently enrolled onto another study and received cord blood-derived NK cells with stem cell infusion.

We excluded these 20 EFS events in a sensitivity analysis to evaluate robustness of the primary EFS analysis. (See below: Sensitivity analysis for EFS).
Four additional subjects received consolidative XRT post-HSCT while in IRC and investigator determined remission in SOC arm.

Axicabtagene ciloleucel arm:
Eight subjects (4%) in the axicabtagene ciloleucel arm were in CR or PR without disease progression per IRC and received NALT. Six subjects were considered as PD following response per investigator and administered NALT (including retreatment with axicabtagene ciloleucel in two subjects). Two additional subjects received consolidative radiation therapy after axicabtagene ciloleucel while in IRC and investigator determined response.

Reviewer comment:
The difference in between the two arms for this event category is primarily driven by the higher rate of discordance between central assessment of responder and investigator assessment of non-responder/PD specific to the SOC arm compared to the axicabtagene ciloleucel arm (11% versus 3%). (See Table 17 describing discordance between central and investigator assessment of ORR).

2. Subjects with SD per IRC and received NALT without disease progression:

SOC Arm:
Twenty-nine subjects (16%) in the SOC arm received NALT while in stable disease (SD) per IRC. Out of these 29 subjects, 15 subjects had best response of PD per investigator assessment, 12

subjects had SD per investigator assessment and 2 subjects had best response of PR followed by PD per investigator assessment. Twenty two out of these 29 subjects had received 2-3 cycles of chemoimmunotherapy. The remainder of seven subjects received only one cycle of chemoimmunotherapy with imaging performed after 1 cycle for clinical suspicion of PD. Investigator determined that 6/7 subjects had best response of PD and one subject had SD.

Reviewer comment:
Administration of NALT for lack of response to 2-3 cycles of protocol specified chemoimmunotherapy is clinically justified. However, seven subjects underwent imaging for disease assessment following only one cycle of chemotherapy. Given the lack of response to single cycle of therapy, NALT was administered. While maximal tumor kill is typically achieved with the first cycle of chemotherapy, It is conceivable that administration of an additional cycle of chemotherapy may have resulted in a response. Therefore, these seven events were excluded from a sensitivity analysis for EFS.

Axicabtagene ciloleucel arm:
One subject (0.5%) in the axicabtagene ciloleucel arm received NALT for investigator determined PD while in IRC determined SD.

Reviewer comment:
The difference between the two arms for this event category is due to the higher rate of SD and PD per investigator assessment observed in SOC arm compared to axicabtagene ciloleucel arm (18% vs. 5% for SD and 33% vs. 8% for PD). Refer to Table 16 for response assessment per IRC and investigator based on treated population.

3. NALT in the absence of any evaluable disease assessment:
SOC Arm:
Ten subjects (6%) in SOC arm received NALT in the absence of any evaluable disease assessment. Out of these 10 subjects:

- Six subjects did not receive any on-study treatment due to subject request in 5 subjects and negative disease biopsy in one subject.
- Three subjects were unable to tolerate investigator selected chemotherapy requiring switch to an alternative regimen (which was considered NALT) prior to any disease assessment and
- One subject had investigator determined PD at Day 150 assessment and initiated NALT. However, IRC determined the response to be undefined due to lack of FDG avid disease at baseline. Therefore, the assessment was considered unevaluable.

Reviewer comment:
The six subjects that were randomized and did not receive any protocol specified therapy, subsequently received anti-lymphoma therapy in the absence of post-baseline imaging. These were considered EFS events at the time of randomization. Since these subjects did not receive any protocol specified therapy, these six events were excluded from EFS sensitivity analysis and

were instead censored at randomization.

Axicabtagene ciloleucel arm:
Two subjects (1%) in axicabtagene ciloleucel arm received NALT in the absence of any evaluable disease assessment. These subjects were not treated with axicabtagene ciloleucel due to study ineligibility (cardiac lymphoma involvement in one subject who was randomized but did not undergo leukapheresis) and Grade 2 ALT increase in another subject who underwent leukapheresis but did not receive LD and CAR T infusion and subsequently received NALT.

Sensitivity analysis for EFS:
We conducted an exploratory post-hoc sensitivity analysis in which 35 events in the SOC arm were excluded from EFS analysis. In total, 35 subjects in the SOC arm were excluded as EFS events and imputed as ongoing responders and censored at the time of data cut off or randomization. Nineteen subjects that were administered NALT based on investigator determined lack of response or PD while in IRC determined response and 7 subjects that were administered NALT while in IRC determined SD after one cycle of chemotherapy were considered ongoing responders and censored at data cut off in the sensitivity analysis. Two subjects had responded (PR) to chemotherapy but were not taken for transplantation and one additional subject was inadvertently enrolled on a different protocol with receipt of off protocol stem cells were included. See Table 14 below for details.

In addition, 6 subjects randomized to the SOC arm who did not receive any protocol specified therapy and subsequently received anti-lymphoma therapy with no post-baseline disease assessment, considered events at randomization in the primary analysis were also excluded as events and instead censored at randomization in the sensitivity analysis.

Table 14. FDA - Categorization of Events Excluded from EFS Sensitivity Analysis

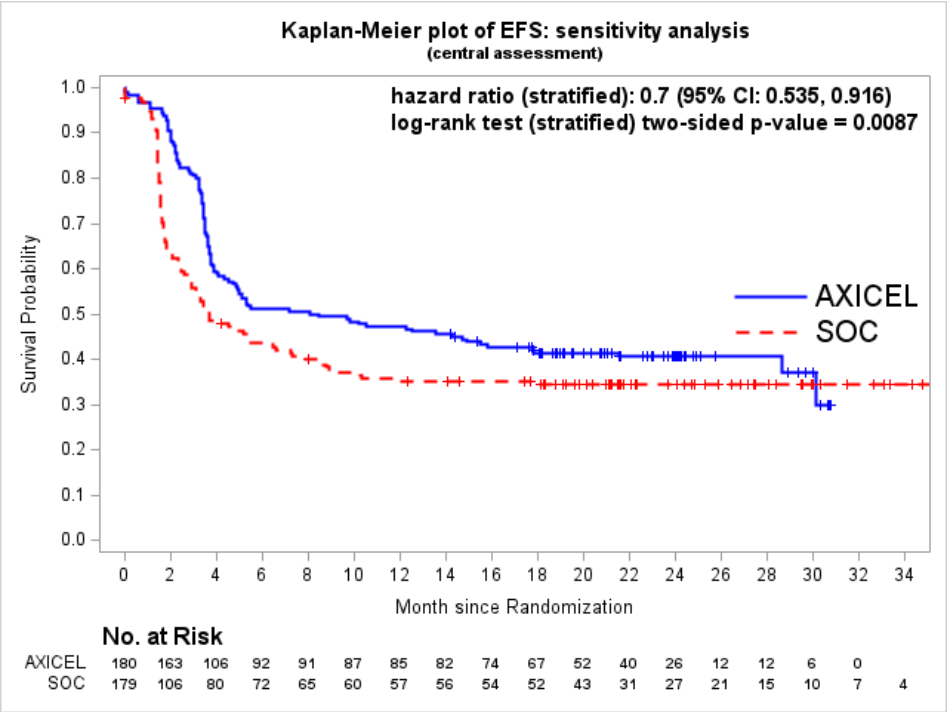
Issue	Number of subjects
Subjects considered non-responders by investigators but responder by IRC assessment and not taken for HSCT and given NALT	14
Responders but progressed prior to HSCT per investigators and given NALT but no progression per IRC	2 (includes one subject who received HSCT as NALT)
Subjects considered PD after HSCT per investigators and given NALT but no PD per IRC	3
Subject inadvertently enrolled on a different protocol with cord blood derived NK cells combined with HDT/HSCT which was considered NALT	1
Unscheduled imaging after one cycle of chemotherapy which showed PD/SD per investigators and SD per IRC and subjects received NALT	7
Subject attained PR per investigator after 2 cycles of chemotherapy but not taken for transplant as institution required CMR	1
Subject attained PR per investigator and IRC after 3 cycles of chemotherapy, not taken for transplant followed by PD	1
Subjects randomized to SOC arm who did not receive any protocol specified therapy, subsequently received anti-lymphoma therapy with no post-baseline disease were considered events	6
Total	35

Source: FDA analysis

Four additional subjects in the SOC arm who were in response post-HSCT per central and investigator assessment received consolidative radiation therapy which constituted events. These remained events in the sensitivity analysis as consolidative radiation therapy while in response was also considered an event in the axicabtagene ciloleucel arm.

The outcome of the sensitivity analysis was consistent with the primary analysis. The stratified log-rank test nominal p value is still significant at .0087. The stratified hazard ratio is 0.7 (95% CI: 0.54, 0.92). Overall results of the sensitivity analysis indicate that EFS benefit observed with the primary efficacy analysis are robust. The KM curve for the sensitivity analysis is demonstrated in Figure 7.

Figure 7. FDA - KM Plot of EFS: Sensitivity Analysis



Source: FDA statistical reviewer

Reviewer comment:

In summary, FDA agrees that the primary endpoint of EFS is significantly improved in the axicabtagene ciloleucel arm compared to the SOC arm. The Applicant proposed to include 2-year EFS rate in the USPI. Given the significant censoring in the axicabtagene ciloleucel arm at 2 years, the 18-month EFS rate is more informative. Through Month 18, eight subjects are censored on axicabtagene ciloleucel arm and 12 subjects were censored on SOC arm. At 18 months, 172 (96%) of axicabtagene ciloleucel subjects and 167 (93%) of SOC subjects were at risk or had already experienced an event indicating that 18-month EFS is reflective of clinical benefit of axicabtagene ciloleucel compared to SOC arm. The estimated 18-month EFS was 41.5% [95% CI: 34.2, 48.6] in the axicabtagene ciloleucel arm and 17% [95% CI: 11.8, 23] in the SOC arm. Section 14 of the USPI will include 18-month EFS rate for ZUMA-7.

The Applicant reports an estimated median follow-up for EFS of 23 months in the axicabtagene ciloleucel arm and 21 months in the standard therapy arm, based on the reverse KM method, and proposed this for inclusion in labeling. Although the calculations are correct, they substantially overestimate the follow-up time due to 70% of subjects having an early event; the actual median follow-up is 3.6 months for both arms combined (source: FDA statistical reviewer). However, because the median EFS was reached in both arms, the follow-up time need not be included in labeling and this information was removed.

Subgroup analysis:
FDA agrees that for the primary endpoint of EFS, consistent results of EFS was observed across most subgroups such as primary refractory versus relapsed disease, high versus low second-line age-adjusted IPI, histological subtype, age, sex etc. FDA agrees that trends in some of the subgroups with small sample size such as African American race and "other" histological subtypes are difficult to substantiate given the small sample size . Therefore, meaningful conclusion regarding efficacy in these subgroups cannot be made.

Efficacy Results –Secondary Endpoints, and Other Relevant Endpoints

Data:

Key Secondary Efficacy Endpoints: ORR and OS

ORR per Blinded Central Assessment
ORR was higher in the axicabtagene ciloleucel arm (83% of subjects) than in the SOCT arm (50% of subjects), with a statistically significant difference in ORR between the treatment arms of 33.1% (95% CI: 23.2%, 42.1%; stratified CMH $p < 0.0001$; odds ratio = 5.31 [95% CI: 3.08, 8.90; stratified CMH test $p < 0.0001$) (Table 15 and Figure 8). The CR rate was numerically higher in the axicabtagene ciloleucel arm (65%) compared with the SOCT arm (32%).

Table 15. Applicant - ORR and Best Overall Response per Blinded Central Assessments (FAS)

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 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)
95% CI for response rate	(0.9, 6.4)	(13.0, 24.9)
Progressive disease, n (%)	21 (12)	38 (21)
95% CI for response rate	(7.4, 17.3)	(15.5, 28.0)
Undefined/ no disease, n (%)	0 (0)	4 (2)
95% CI for response rate	(0.0, 2.0)	(0.6, 5.6)
Not evaluable, n (%)	0 (0)	0 (0)
95% CI for response rate	(0.0, 2.0)	(0.0, 2.0)
Not done, n (%)	4 (2)	14 (8)
95% CI for response rate	(0.6, 5.6)	(4.3, 12.8)

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; ORR, objective response rate; PR, partial response.
Notes: 95% CI for rate is from the Clopper-Pearson method, and the 95% CI for the difference in ORR (standard of care arm as reference group) is from Wilson's score method with continuity correction.
Response assessments per Lugano Classification {Cheson 2014}.
The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system.
One-sided p-value from CMH test is presented.
"Undefined/no disease" include subjects who were found to have no disease at baseline or follow-up by central assessment but had disease by investigator assessment. "Not evaluable" disease assessment were performed but no conclusion could be made.
Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Table 14.

Concordance between the investigator and blinded central assessment of ORR was high at 89% (κ = 0.76; 95% CI: 0.69, 0.83).

Sensitivity analysis of ORR per investigator assessment was consistent with the ORR results based on blinded central assessment, with a difference in ORR between arms of 38.1% (95% CI: 28.1%, 47.0%).

Results overserved in a subgroup analysis of ORR per blinded central assessment were comparable.

The FDA's Assessment:

Key Secondary Endpoints:

1. Overall response rate (ORR):
FDA agrees with the Applicant's assessment that axicabtagene ciloleucel arm had statistically significantly higher ORR compared to SOC arm with difference in ORR between the two treatment arms of 33% (95% CI:23%, 42%) and the CMH test p-value <0.0001. This difference in ORR was driven primarily by a higher CR rate of 65% (95% CI: 58, 72) in axicabtagene ciloleucel arm compared to 32% (95% CI: 26, 40) in the SOC arm.

ORR in the treated population based on central and investigator assessment is outlined below:

Table 16. FDA - ORR and Best Overall Response of Treated Population

Response category	**Axicabtagene ciloleucel Arm N=170**		**SOC Arm N=168**	
	Investigator	IRC	Investigator	IRC
Number of responders (CR+PR), n (%)	148 (87%)	149 (88%)	80 (48%)	90 (53.5%)
CR, n (%)	109 (64%)	116 (68%)	61 (36%)	58 (34.5%)
PR, n (%)	39 (23%)	33 (19%)	19 (11%)	32 (19%)
SD, n (%)	9 (5%)	5 (3%)	30 (18%)	33 (20%)
PD, n (%)	13 (8%)	16 (9%)	55 (33%)	38 (23%)
ND, n (%)	0	0	3 (2%)	3 (2%)
Indeterminate response, n (%)				4 (2%)

Source: FDA analysis of ADEFF dataset

The overall concordance between central assessment and investigator assessment for ORR was

94% in axicabtagene ciloleucel arm and 84% in the SOC arm.

Table 17. FDA - Discordance between IRC and Investigator Assessment of Response

Discordance	Axicabtagene ciloleucel arm N=180	SOC arm N=179
Objective responder discordance	11 (6%)	28 (16%)
Central assessment=R Investigator assessment=NR	6 (3%)	19 (11%)
Central assessment=NR Investigator assessment=R	5 (3%)	9 (5%)

Source : BLA 125643/394, Module 5.3
R=Responder, NR=Not Responder

There is skewed discordance in the SOC arm compared to the axicabtagene ciloleucel arm (11% vs. 3%) for the subgroup of responder per central assessment and non-responder per investigator assessment.
The major categories of discordant reads were:
1. Best overall response of SD by investigator assessment but PR by central assessment.(14 cases)
2. Best overall response of PD by investigator but PR by central assessment. (5 cases)

Main reason for discordance include discrepancy in the Deauville five-point score (5PS) which is a qualitative visual interpretation of the FDG uptake. For example, 5 PS remained 5 post - treatment with no change compared to baseline per investigator assessment, however, per central assessment, 5 PS score at baseline either decreased to 4 or remained 5 post-treatment with reduced FDG uptake constituting a partial metabolic response. In addition, in some cases, 5PS decreased from 5 to 4 per investigator assessment but was not considered clinically meaningful given lack of response on CT scans. Most of these cases required adjudication by the IRC indicating that there was lack of concordance even between the central radiologists. (Source: Applicant IR Dated February 10, 2022).

Reviewer comment:
While the lack of a predefined standardized reduction in metabolic uptake required for partial metabolic response in Lugano classification coupled with reliance on subjective visual interpretation of Deauville 5PS could result in discrepant radiological assessments, the reason why such a discordance was limited to the SOC arm is not clearly understood. It may be related to 1) inability of chemotherapy to induce a deep response resulting in modest reduction in SUV which may be subject to variable interpretation 2) element of bias in an open label trial comparing a novel therapy such as CAR T to a more traditional chemotherapy followed by

HDT/HSCT approach.

Notwithstanding this discordance, both central and investigator assessment of response demonstrated higher ORR and CR rate in the axicabtagene ciloleucel arm and a higher rate of SD and PD as best response in the SOC arm.

Data:

Overall Survival

For ZUMA-7, the first interim analysis occurred at approximately 73% (corresponding to 153 events) information as against the originally planned 52% (corresponding to 110 events) and will be followed by the final analysis, that is expected to occur when 210 events are observed or no later than 5 years after the first subject is randomized. There will no longer be a second interim analysis prior to the final analysis.

At the time of the data cutoff, 72 subjects (40%) in the axicabtagene ciloleucel arm and 81 subjects (45%) in the SOCT arm had died (stratified HR of 0.730 [95% CI: 0.530, 1.007]). In the axicabtagene ciloleucel arm the KM estimated median OS had not been reached with a median follow-up time for OS (reverse KM approach) of 24.7 months (95% CI: 23.3, 26.0). In the SOCT arm the KM estimated median OS was 35.1 months with a median follow-up time for OS of 24.1 month (95% CI: 22.1, 25.1) (Table 18 and Figure 8).

While the data are still immature, the interim analysis of OS favored axicabtagene ciloleucel over SOCT, but the difference between the treatment arms was not statistically significant (p = 0.027 with a 1-sided alpha of 0.004 allocated to the interim OS analysis).

Table 18. Applicant - OS (FAS; Interim Analysis)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Number of subjects	180	179
Death from any cause, n (%)	72 (40)	81 (45)
Alive, n (%)	108 (60)	98 (55)
Full consent withdrawn	0 (0)	9 (5)
Lost to follow up	2 (1)	2 (1)
End of study due to investigator decision	0 (0)	1 (1)
End of study due to other reason	0 (0)	0 (0)
Stratified log-rank p-value	0.0270	NA
Hazard ratio (95% CI), stratified	0.730 (0.530, 1.007)	NA
Unstratified log-rank p-value	0.0442	NA

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Hazard ratio (95% CI), unstratified	0.759 (0.553, 1.043)	NA
KM median (95% CI) OS time (months)	NR (28.3, NE)	35.1 (18.5, NE)
Min, Max OS time (months)	1, 38+	0+, 37+
Survival rate % (95% CI) by KME		
6 month	90.0 (84.6, 93.6)	87.1 (81.0, 91.3)
12 month	76.0 (69.1, 81.6)	64.7 (57.0, 71.4)
24 month	60.7 (52.8, 67.7)	52.1 (44.0, 59.5)
36 month	53.1 (43.1, 62.2)	33.7 (10.0, 59.9)
Median (95% CI) follow-up time (months) (reverse KM approach)	24.7 (23.3, 26.0)	24.1 (22.1, 25.1)

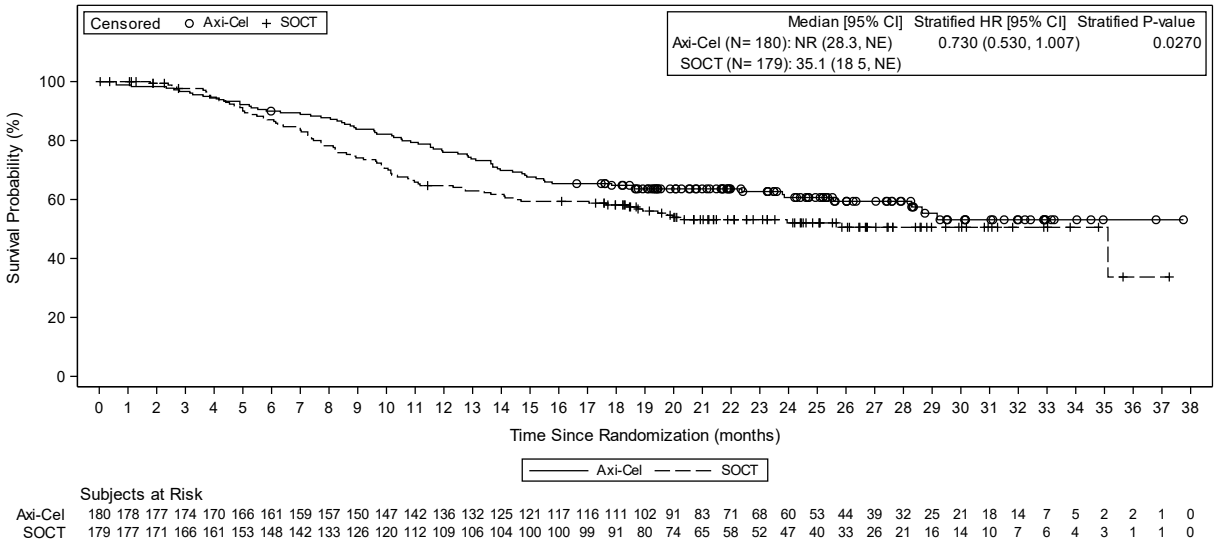
Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; NR, not reached; OS, overall survival.

Notes: OS is defined as the time from the randomization date to the date of death from any cause. Subjects who did not die by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

Source: Modified from m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 16.

Figure 8. Applicant - KM Plot of OS (FAS; Interim Analysis)



Data cutoff date = 18MAR2021.
Abbreviations: Axicabtagene ciloleucel, axicabtagene ciloleucel; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NE, not estimable; NR, not reached; OS, overall survival; SOCT, standard of care therapy.
Notes: OS is defined as the time from the randomization date to the date of death from any cause. Subjects who did not die by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log rank test is presented. Event/Censoring time was calculated as Event/Censoring date – Randomization date +1 (= days) / 30.4375 (= months).
Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Figure 8

Although there was no planned crossover between treatment arms, subjects who did not respond to SOCT could receive subsequent treatment for lymphoma deemed appropriate by the investigator, such as non-study specific chemotherapy, immunotherapy, targeted agents, as well as anti-CD19 CAR T-cell therapy off protocol. Of the 179 subjects randomized to the SOCT arm, 100 subjects (56%) later received commercially available or investigational cell therapy as new lymphoma therapy after SOCT (ie, treatment switching rate). Prespecified sensitivity analyses of OS were performed to address the confounding effects from subsequent cell therapy in the SOCT arm. The sensitivity analysis results reinforced the positive trend seen for OS in the FAS:

- Rank Preserving Structural Failure Time model {Robins 1991}: stratified HR of 0.580 (95% CI: 0.416, 0.809).
- Inverse Probability of Censoring Weights model {Robins 2000}: HR of 0.695 (95% CI: 0.461, 1.049).

Subjects will continue to be followed-up and the primary (final) OS analysis will be performed.

The FDA's Assessment:

Overall survival:
The OS analysis was a prespecified interim analysis. OS data for 12 subjects (7%) from SOC arm and 2 subjects(1%) from axicabtagene ciloleucel arm was missing due to study discontinuation. Statistical reviewer requested updated vital records from publicly available sources for these subjects. Based on the updated information, the OS data was updated to include four deaths that had occurred in the SOC arm prior to the data cut-off date of March 18, 2021. All four subjects had disease progression events per central assessment prior to study discontinuation. Therefore, this additional information of four deaths does not change the EFS or PFS analysis. Four additional subjects were confirmed to be alive at the data cutoff date; three in the SOC arm (including one death in the SOC arm that occurred after the data cutoff date) and one in the axicabtagene ciloleucel arm. For the remaining 6 subjects, the updated vital record remains unknown at the data cut off due to lack of information in public records.

At an estimated median follow up of 19.4 months, 40% of the subjects in the axicabtagene ciloleucel arm and 47% of the subjects in the SOC arm have died. OS data is at 75% information fraction as 157 out of 210 deaths have occurred. Final OS analysis will occur when 210 deaths have occurred.

The table below includes the updated OS data:

Table 19. FDA - Overall Survival in ZUMA-7

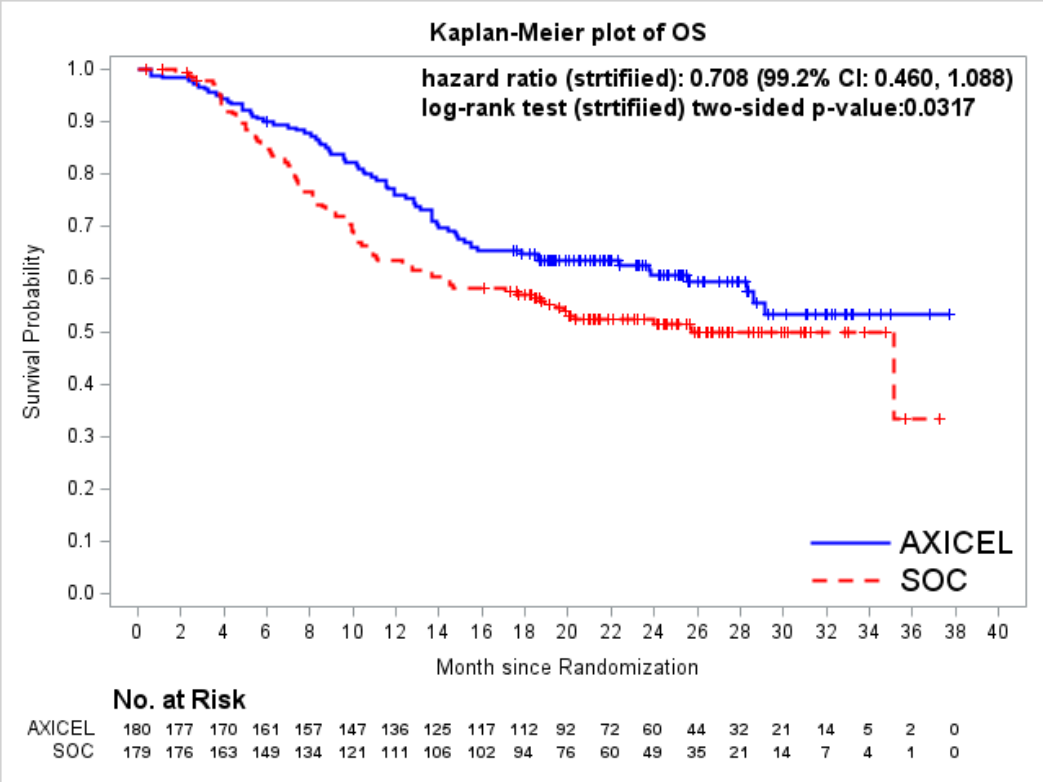
Parameter	Axicabtagene ciloleucel arm N=180	SOC arm N=179
Death from any cause, n(%)	72 (40%)	85 (47%)
Alive, n(%)	106 (59%)	86 (48%)
Full consent withdrawn, n(%)	0	6 (3%)
Lost to follow up, n(%)	2 (1%)	2 (1%)
KM median (95% CI)	NR (28.3, NE)	25.7 (17.6, NE)
Stratified Hazard Ratio (99.1% CI)	0.71 (0.46, 1.1)	
Stratified log-rank test two-sided p-value	0.03	
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)
15 month	67.6 (60.3, 74.0)	58.3 (50.6, 65.2)
18 month	64.8 (57.3, 71.3)	57.1 (49.4, 64.1)
21 month	63.6 (56.1, 70.2)	52.4 (44.6, 59.6)
24 month	60.7 (52.8, 67.7)	51.3 (43.4, 58.7)

Data Cutoff date: March 18, 2021. Source: FDA statistical reviewer

The stratified hazard ratio (99.1% CI) was 0.71 (0.46, 1.1) with a stratified log-rank two sided p-value of 0.03. This interim analysis for OS is premature given the heavy censoring around 18 months (Refer to Figure 9 below). Overall, the difference in OS was not statistically significant due to failure to cross the prespecified boundary of p-value of 0.0087 given the alpha allocation for interim analysis.

Figure 9. FDA - KM Plot of OS



Source: FDA statistical reviewer

Reviewer comment:

While the difference in OS between the two arms is not statistically significant, the direction of the observed treatment effect is consistent with the EFS and PFS data. There is no detriment to OS with the second line use of axicabtagene ciloleucel compared to SOC. Results of the OS analysis may be confounded by the fact that 55% of the subjects randomized to SOC arm received autologous CD19-directed CAR T therapy after experiencing an event.

Data

Other Secondary Endpoints

Per investigator assessment, 243 EFS events occurred, compared with 252 EFS events per blinded central assessment. The overall concordance between the blinded central assessment and investigator's assessment of EFS events was high (97%; κ = 0.94, 95% CI: 0.90, 0.98). EFS per investigator assessment was consistent with the primary EFS analysis per blinded central assessment with a stratified HR of 0.404 (95% CI: 0.311, 0.525). The KM median EFS time was longer in the axicabtagene ciloleucel arm (10.8 months [95% CI: 5.0, 28.6]) than in the SOCT arm (2.3 months [95% CI: 1.7, 3.1]).

Subgroup analyses of EFS per investigator assessment were also consistent with the subgroup analysis of EFS per blinded central assessment.

Progression-free Survival

The KM median PFS time based on the investigator assessment was longer in the axicabtagene ciloleucel arm compared with the SOCT arm (14.7 months [95% CI: 5.4, not estimable] versus 3.7 months [95% CI: 2.9, 5.3]) (stratified HR of 0.490 [95% CI: 0.368, 0.652]). The median follow-up time for PFS using the reverse KM method was 22.6 months (95% CI: 20.8, 24.0) in the axicabtagene ciloleucel arm and 19.6 months (95% CI: 14.6, 21.2) in the SOCT arm (Table 20).

Table 20. Applicant - PFS per Investigator Assessment (FAS)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Number of subjects	180	179
Events, n (%)	96 (53)	103 (58)
Censored, n (%)	84 (47)	76 (42)
Stratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), stratified	0.490 (0.368, 0.652)	NA
Unstratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), unstratified	0.524 (0.396, 0.694)	NA
KM median (95% CI) PFS time (months)	14.7 (5.4, NE)	3.7 (2.9, 5.3)
Min, Max PFS time (months)	0+, 31+	0+, 33+

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Event		
Disease progression, n (%)	85 (47)	98 (55)
Death from any cause, n (%)	11 (6)	5 (3)
Censoring reason		
Response ongoing, n (%)	79 (44)	34 (19)
New lymphoma therapy, n (%)	5 (3)	37 (21)
No post-baseline disease assessment, n (%)	0 (0)	1 (1)
Full withdrawal of consent, n (%)	0 (0)	2 (1)
Lost to follow up, n (%)	0 (0)	2 (1)
Progression-free rate, % (95% CI) by KME		
6 month	57.2 (49.6, 64.2)	39.3 (31.1, 47.3)
12 month	52.1 (44.4, 59.2)	28.2 (20.8, 36.2)
24 month	45.7 (38.1, 53.0)	27.4 (20.0, 35.3)
Median (95% CI) follow-up time (months) (reverse KM approach)	22.6 (20.8, 24.0)	19.6 (14.6, 21.2)

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; FAS, Full Analysis Set; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; PFS, progression-free survival; SCT, stem cell transplant.
Notes: PFS is defined as the time from the randomization date to the date of disease progression or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including SCT in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever is earlier. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).
Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Table 19

PFS as determined by the investigator assessment was further analyzed in subgroups defined by selected baseline demographic and disease characteristics. Across the majority of subgroups PFS was consistent with the FAS, favoring axicabtagene ciloleucel over SOCT.

The FDA's Assessment:
PFS per central assessment: PFS per investigator assessment was secondary endpoint for ZUMA-7. However, given that EFS and ORR per central assessment were utilized for efficacy analysis, the review team analyzed PFS per central assessment to be consistent. This would also

allow for assessment of efficacy without investigator bias.

PFS (central assessment) is summarized below:

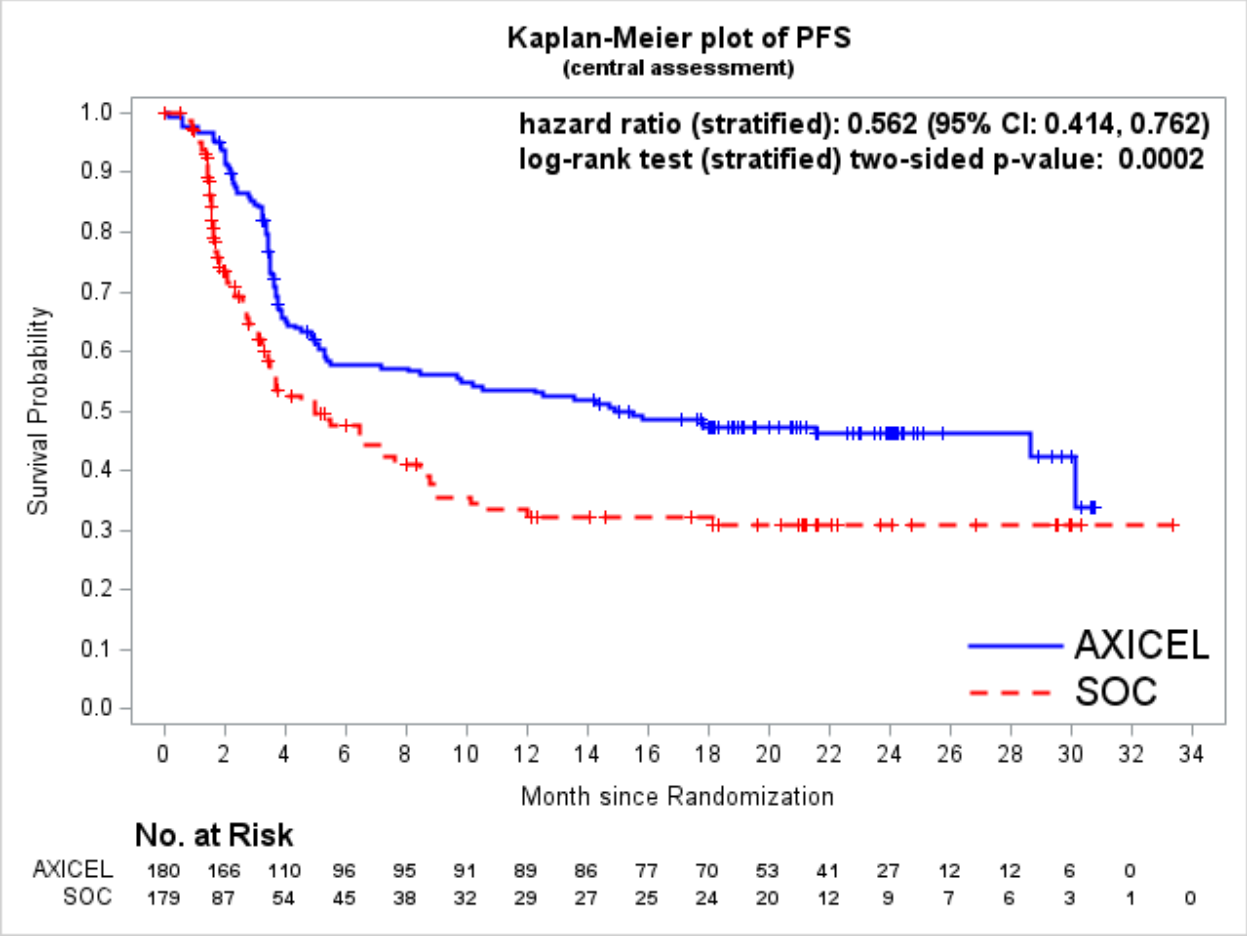
Table 21. FDA - PFS per Central Assessment

Characteristics	Axicabtagene ciloleucel arm N=180	SOC arm N=179
PFS Events, n(%)	93 (52%)	81 (45%)
Censored, n(%)	87 (48%)	98 (55%)
PFS Hazard ratio (95% CI), stratified	0.56 (0.41, 0.76)	
Stratified log-rank test, two-sided p value	0.0002	
Median PFS (95% CI), mo, by KM estimate	14.9 (7.2, NE)	5.0 (3.4, 8.5)
PFS Event		
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)
PFS rate, % (95% CI) by KM estimate		
6 month	57.8 (50.1, 64.8)	47.5 (38.2, 56.3)

Characteristics	Axicabtagene ciloleucel arm N=180	SOC arm N=179
12 month	53.6 (45.8, 60.7)	32.3 (23.5, 41.4)
18 month	47.3 (39.6, 54.7)	32.3 (23.5, 41.4)

Source: FDA statistical reviewer

Figure 10. FDA - KM Plot of PFS (Central Assessment)



Source: FDA statistical reviewer

Reviewer comment:

It is noted that the total number of PFS events are higher in the axicabtagene ciloleucel arm compared to the SOC arm which is contrary to the EFS event analysis. This is due to the exclusion of NALT from the definition of PFS events given that the main difference in EFS events was driven by high rate of NALT in the SOC arm. The median PFS and 12-month PFS is longer in the axicabtagene ciloleucel arm compared with SOC arm due to delayed occurrence of disease

progression events (See Table 21). Therefore, majority of censoring in the axicabtagene ciloleucel arm is due to ongoing responses and is observed in the tail of the KM curve while censoring in the SOC arm is primarily due to NALT and observed early in the KM curve. In summary, while there is no prespecified statistical testing for PFS, the PFS data support the clinical efficacy of axicabtagene ciloleucel compared to SOC and is consistent with EFS and ORR data.

Data

Duration of Response

The median DOR per blinded central assessment among responders was longer in the axicabtagene ciloleucel arm at 26.9 months (95% CI: 13.6, not estimable) compared with the SOCT arm at 8.9 months (95% CI: 5.7, not estimable) (stratified HR of 0.736 [95% CI: 0.488, 1.108]), with a median follow-up time for DOR using the reverse KM method of 19.5 months and 17.3 months, respectively (Table 22).

Table 22. Applicant - DOR per Blinded Central Assessment (FAS)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Number of objective responders (CR + PR)	150	90
Events, n (%)	66 (44)	37 (41)
Censored, n (%)	84 (56)	53 (59)
Stratified log-rank p-value	0.0695	NA
Hazard ratio (95% CI), stratified	0.736 (0.488, 1.108)	NA
Unstratified log-rank p-value	0.1442	NA
Hazard ratio (95% CI), unstratified	0.805 (0.537, 1.205)	NA
KM median (95% CI) DOR (months)	26.9 (13.6, NE)	8.9 (5.7, NE)
Min, Max DOR (months)	0+, 29+	0+, 32+
Events		
Disease progression, n (%)	58 (39)	34 (38)
Death from any cause, n (%)	8 (5)	3 (3)
Censoring reasons		
Response ongoing, n (%)	76 (51)	28 (31)
New lymphoma therapy, n (%)	6 (4)	23 (26)
Subsequent stem cell transplant, n (%)	0 (0)	1 (1)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Axicabtagene ciloleucel retreatment, n (%)	2 (1)	0 (0)
Lost to follow up, n (%)	0 (0)	1 (1)
Event-free rate, % (95% CI) by KME		
6 month	66.8 (58.4, 73.8)	58.9 (46.4, 69.5)
12 month	60.9 (52.4, 68.4)	47.6 (35.2, 58.9)
24 month	54.0 (45.1, 62.0)	45.6 (33.2, 57.1)
Median (95% CI) follow-up time (months) (reverse KM approach)	19.5 (18.2, 21.7)	17.3 (12.7, 19.6)

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; FAS, Full Analysis Set; IxRS, interactive voice/web response system; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA; not applicable; NE, not estimable; PR, partial response.

Notes: Percentages are based on number of subjects in the analysis set with objective response. DOR is defined as the time from the first objective response to disease progression per Lugano Classification {Cheson 2014} or death from any cause. Subjects not meeting the criteria by the analysis data cutoff date will be censored at their last evaluable disease assessment date prior to the data cutoff date or new lymphoma therapy start date (including stem cell transplant in the axicabtagene ciloleucel arm or retreatment of axicabtagene ciloleucel), whichever is earlier. Response assessments per Lugano Classification {Cheson 2014}. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via IxRS. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

Source: Modified from m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 21.

DOR as determined by blinded central assessment was further analyzed in subgroups defined by selected baseline demographic and disease characteristics. Subgroup analysis of DOR was consistent with the FAS.

Sensitivity analysis of DOR based on investigator assessment was consistent with the DOR analysis based on the blinded central assessment.

The FDA's Assessment:

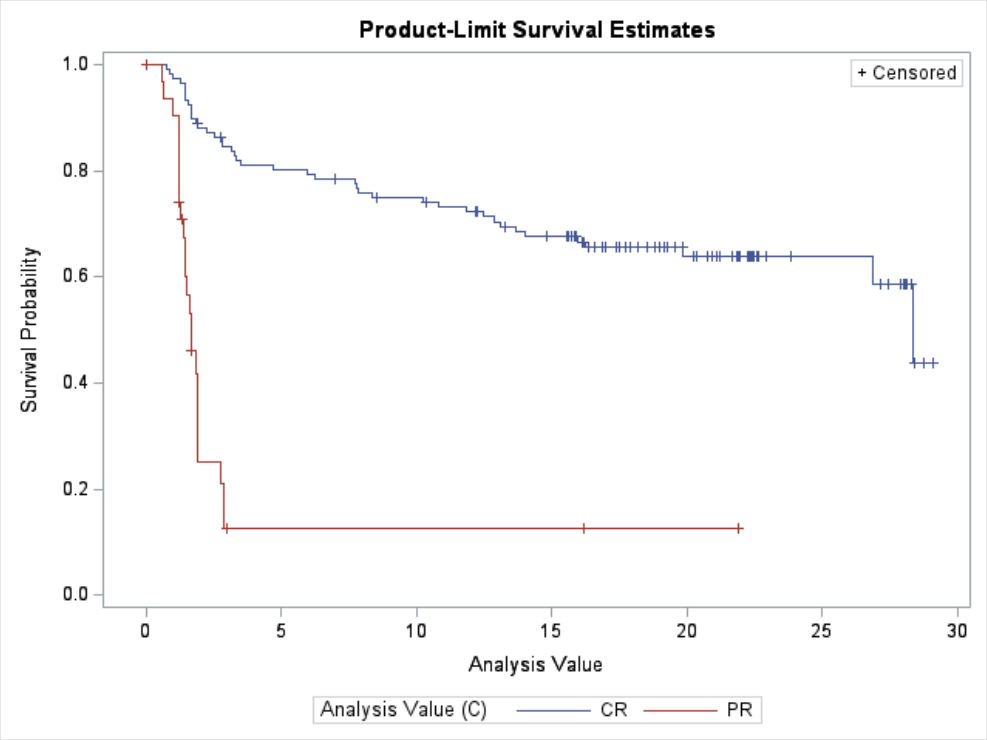
The comparison of DOR between the two arms is a responder analysis that does not compare a population that is well balanced in terms of prognostic factors. Therefore, the review team does not agree with such a comparative analysis and recommends excluding it from the efficacy section of the USPI. Instead, a stand-alone analysis of DOR in the axicabtagene ciloleucel arm was performed to evaluate the DOR in CR compared to PR subjects.

Table 23. FDA - Duration of Response Based on Depth of Response

Parameter	Axicabtagene ciloleucel arm: Responders per IRC in FAS (n=150)	CR (n=117)	PR (n=33)
Median DOR (95% CI)	26.9 mo (13.6, NE)	28.4 mo (26.9, NE)	1.6 mo (1.4, 1.9)
1 year DOR rate (95% CI)	61% (52, 68)	72% (63, 79.5)	13% (3, 28.5)

Source: FDA statistical reviewer

Figure 11. FDA - KM Plot of DOR in CR vs. PR in Axicabtagene Ciloleucel Arm



Source: FDA statistical reviewer

Reviewer comment:
Similar to the third line r/r LBCL setting, the DOR correlates with the depth of response in the second-line setting and primarily CRs are durable in the axicabtagene ciloleucel arm. This information will be included in the USPI to inform prescribers.

Data

Modified Event-free Survival
mEFS was defined the same way as EFS, except that SD as the best response by Study Day 150 assessment was not considered an event.

Based on the blinded central assessment of mEFS, 104 subjects (58%) in the axicabtagene ciloleucel arm and 144 subjects (80%) in the SOCT arm had had an event at the time of the data cutoff (stratified HR of 0.376 [95% CI: 0.290, 0.487]). The KM median mEFS was longer in the axicabtagene ciloleucel arm (10.3 months [95% CI: 5.0, 21.5]) than in the SOCT arm (2.0 months [95% CI: 1.6, 2.8]) (Table 24).

Table 24. Applicant - mEFS by Blinded Central Assessment (FAS)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Number of subjects	180	179
Events, n (%)	104 (58)	144 (80)
Censored, n (%)	76 (42)	35 (20)
Stratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), stratified	0.376 (0.290, 0.487)	NA
Unstratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), unstratified	0.399 (0.309, 0.514)	NA
KM median (95% CI) mEFS time (months)	10.3 (5.0, 21.5)	2.0 (1.6, 2.8)
Min, Max mEFS time (months)	0, 31+	0+, 33+
Event		
Disease progression, n (%)	82 (46)	75 (42)
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)
Best response of SD up to and including Day 150 assessment post-randomization, n (%)	4 (2)	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)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Event-free rate, % (95% CI) by KME		
6 month	53.3 (45.8, 60.3)	26.6 (20.2, 33.3)
12 month	49.4 (42.0, 56.5)	17.6 (12.3, 23.6)
24 month	42.7 (35.3, 49.9)	16.3 (11.1, 22.2)
Median (95% CI) follow-up time (months) (reverse KM approach)	22.8 (20.9, 24.0)	21.2 (20.4, 23.7)

Data cutoff date = 18MAR2021.
Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; mEFS, modified event-free survival; Min, minimum; NA, not applicable; NE, not estimable; SCT, stem cell transplant; SD, stable disease.
Notes: mEFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014} commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. Having SD as the best response by Day 150 assessment post-randomization will not be considered as an event. The stratification factors are response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).
Source: Modified from m5.3.5.1, ZUMA-7 Primary Analysis CSR, Table 9.

mEFS using the blinded central assessment of response in the FAS was further analyzed in subgroups defined by selected baseline demographic and disease characteristics. Across the majority of subgroups, axicabtagene ciloleucel was favored over SOCT, consistent with the FAS.

Based on the investigator assessment of mEFS, 101 subjects (56%) in the axicabtagene ciloleucel arm and 140 subjects (78%) in the SOCT arm had had an event at the time of the data cutoff (stratified HR of 0.393 [95% CI: 0.302, 0.512]). The KM median mEFS was longer in the axicabtagene ciloleucel arm (12.6 months [95% CI: 5.0, 30.2]) than in the SOCT arm (2.3 months [95% CI: 1.7, 3.1]).

The FDA's Assessment:
Since only 4 events in the axicabtagene ciloleucel arm and none in the SOC arm were due to the best response of SD up to and including Day 150 assessment post-randomization, excluding these events and instead censoring these four subjects did not result in any meaningful difference in the outcome of mEFS compared to EFS. In summary, the result of modified EFS is consistent with the primary efficacy analysis of EFS.

The Applicant's Position:

ZUMA-7 demonstrated superior efficacy of axicabtagene ciloleucel as a second-line therapy in adult subjects with r/r LBCL compared with SOCT.

Axicabtagene ciloleucel demonstrated a statistically significant improvement in ORR with ORR rates of 83% in the axicabtagene ciloleucel arm and 50% in the SOCT arm. Given that objective response is a prerequisite to reach HDT-auto-SCT, the ORR translates into at least 50% of subjects in the SOCT arm not being able to reach definitive therapy. The CR rate was 2-fold higher in the axicabtagene ciloleucel arm (65%) compared with the SOCT arm (32%). Median PFS and DOR were also both longer in the axicabtagene ciloleucel arm compared with the SOCT arm.

Overall, nearly 3-fold the percentage of subjects in the axicabtagene ciloleucel arm (94%) were able to reach definitive therapy compared with the SOCT arm (36%). Although the same percentage of subjects in each arm (94%) received the first dose of assigned therapy (axicabtagene ciloleucel or salvage chemotherapy), 55% of the subjects in the SOCT arm either did not complete the planned 2 or 3 cycles (reasons included AEs, disease progression, lack of response, and subject withdrawal), or did not respond to, salvage chemotherapy and therefore could not proceed to HDT-auto-SCT. Another 9% of subjects did not proceed to HDT-auto-SCT after completing salvage chemotherapy, primarily due to disease progression. The 36% of subjects in the SOCT arm who received HDT-auto-SCT compares with 35% of patients in the ORCHARRD study who received auto-SCT {van Imhoff 2017b}.

Based on simulations of outcomes from the ORCHARRD and CORAL studies with SOCT {Gisselbrecht 2010, van Imhoff 2017a}, the prespecified median OS in the SOCT arm was assumed to be 15.8 months. The ZUMA-7 interim OS results suggested a trend favoring axicabtagene ciloleucel (median OS had not been reached) over SOCT (median OS of 35.1 months). The median OS observed in the SOCT arm should be considered in the context of subsequent therapies. In ZUMA-7, subjects who did not respond to SOCT could receive any subsequent treatment for lymphoma deemed appropriate by the investigator, such as non-study specific chemotherapy, immunotherapy, targeted agents, as well as cell therapy off protocol. Although there was no planned crossover between treatment arms, 56% of subjects in the SOCT arm received subsequent cell therapy after SOCT (ie, treatment switching rate). Prespecified sensitivity analyses of OS to account for the treatment switching rate were consistent with the OS results in the FAS and reinforced the positive trend of OS benefit provided by axicabtagene ciloleucel over SOCT.

The FDA's Assessment:
Please refer to FDA's assessment under Integrated Assessment of Effectiveness (Section 8.1.4).

Dose/Dose Response
Data:

Of 170 subjects who received axicabtagene ciloleucel infusion, 162 were evaluable for levels of anti-CD19 CAR T-cells between Treatment day 0 and 4 weeks post-treatment.

Numerically higher anti-CD19 CAR T-cell levels in blood (median peak and AUC_{0-28}) were associated with subjects who had a response (CR or PR; 142 subjects) to axicabtagene ciloleucel treatment compared with subjects who did not respond (SD or PD; 20 subjects). The median peak and AUC_{0-28} anti-CD19 CAR T-cell levels were higher for subjects who responded compared

with those who did not respond (peak: 28.94 cells/µL vs. 10.45 cells/µL, respectively; AUC_{0-28}: 292.86 cells/µL•day vs 70.14 cells/µL•days, respectively).

Subjects who achieved a CR (109 subjects) as best overall response had numerically higher median peak anti-CD19 CAR T-cell levels and AUC_{0-28} in blood compared with subjects whose best response was PR (33 subjects). For subjects who achieved CR as best response compared with subjects who achieved PR as best response, the median peak anti-CD19 CAR T-cell level was 32.33 cells/µL and 22.30 cells/µL, respectively; and the median AUC_{0-28} was 322.18 cells/µL•day and 279.16 cells/µL•day, respectively.

Details of explored possible associations between axicabtagene ciloleucel pharmacokinetics and clinical response outcomes are provided in m5.3.4.2, ZUMA-7 Primary Analysis Pharmacokinetics and Pharmacodynamics Report, Section 2.6.1.

The Applicant's Position:

Numerically higher anti-CD19 CAR T cell levels (peak and AUC0-28) were associated with subjects who were responders (CR or PR; n = 142) compared with subjects who were nonresponders (SD or PD; n = 20). Median anti-CD19 CAR T-cell peak and AUC_{0-28} were numerically higher in subjects whose best response was CR (n = 109) compared with subjects whose best response was PR (n = 33).

The FDA's Assessment:
FDA agrees with Applicant's assessment. Refer to the Clinical Pharmacology review.

Durability of Response/Persistence of Effect

The Applicant's Position:

Data on durability of response are provided in the Efficacy Results – EFS Subgroup Analysis, Secondary Endpoints, and Other Relevant Endpoints section.

The FDA's Assessment:
See FDA assessment under Duration of Response.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Data:

EORTC QLQ-C30 Global Health Status

Baseline (screening visit) mean EORTC QLQ-C30 global health status scores for evaluable subjects in the QoL analysis set were comparable between the axicabtagene ciloleucel (68.6 [95% CI: 65.6, 71.7]) and SOCT (70.1 [95% CI: 66.1, 74.1]) arms.

There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 18.1 [95% CI: 12.3, 23.9]; adjusted $p < 0.0001$) in favor of axicabtagene ciloleucel. This difference was also statistically significant at Study Day 150 (estimated difference 9.8 [95% CI: 2.6, 17.0]; adjusted $p = 0.0124$). Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 100 for the axicabtagene ciloleucel arm versus at Month 9 for the SOCT arm.

EORTC QLQ-C30 Physical Functioning

Baseline (screening visit) mean EORTC QLQ-C30 physical functioning scores for evaluable subjects in the QoL analysis set were comparable between the axicabtagene ciloleucel (83.5 [95% CI: 80.8, 86.2]) and SOCT (85.3 [95% CI: 82.0, 88.6]) arms.

There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 13.1 [95% CI: 8.0, 18.2]; adjusted $p < 0.0001$) in favor of axicabtagene ciloleucel. Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 150 for the axicabtagene ciloleucel arm versus at Month 12 for the SOCT arm.

EQ-5D-5L VAS

Baseline (screening visit) mean EQ-5D-5L VAS scores were comparable between the axicabtagene ciloleucel (72.4 [95% CI: 69.5, 75.2]) and SOCT (74.4 [95% CI: 70.9, 77.9]) arms. There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 (estimated difference 13.7 [95% CI: 8.5, 18.8]; adjusted $p < 0.0001$) and Study Day 150 (estimated difference 11.3 [95% CI: 5.4, 17.1]; adjusted $p = 0.0004$) in favor of axicabtagene ciloleucel. Mean estimated scores had numerically returned to or exceeded scores at baseline by Study Day 100 for the axicabtagene ciloleucel arm versus Month 9 in the SOCT.

The Applicant's Position:

In addition to efficacy outcomes, QoL is a major concern for patients with cancer and the patient's subjective experience needs to be assessed to define the overall benefits of a treatment. The prespecified PRO endpoints evaluated showed that treatment with axicabtagene ciloleucel improves QoL compared with SOCT, as demonstrated by a statistically significant and clinically meaningful difference in mean change of scores from baseline to Study Day 100 for EORTC QLQ-C30 global health and physical functioning, and EQ-5D-5L VAS. The data also suggest faster recovery to screening QoL with axicabtagene ciloleucel compared with SOCT.

The FDA's Assessment:

ZUMA-7 was an open-label study. Patient-reported outcomes in an open-label study may be impacted by the subjects' knowledge of the treatment received. In addition, EORTC QLQ-C30 and EQ-5D-5L VAS are currently not validated for patients with DLBCL. Results of any

exploratory analysis conducted by the Applicant should be interpreted with caution. Notably, the Applicant does not intend to include PRO data in labeling. Therefore, PRO data, namely EORTC QLQ-C30 global health status and physical functioning and EQ-5D-5L VAS were not reviewed in this submission.

Additional Analyses Conducted on the Individual Trial

Data:

No other analyses were conducted for ZUMA-7.

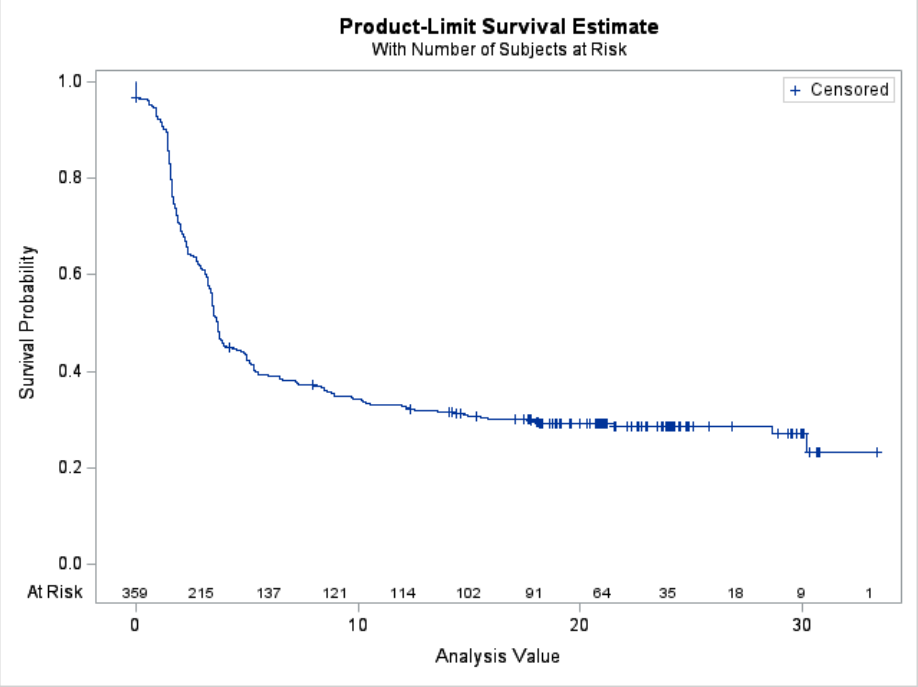
The Applicant's Position:

Not applicable.

The FDA's Assessment:

Outcome of subjects in the SOC arm that underwent HDT/HSCT:
To understand the outcome of the subgroup that underwent HSCT, the review team analyzed the EFS of the 62 subjects that underwent transplantation in the SOC arm. The intent of this exploratory subgroup analysis is not to compare the outcome of the transplanted subgroup with the axicabtagene ciloleucel arm given that this is not a randomized comparison and since the two groups are not comparable in terms of baseline characteristics. Subjects that underwent HSCT were more likely to have relapsed disease (37% vs. 26%) and ECOG score of 0 (68% vs. 53%) compared to the axicabtagene ciloleucel arm. Instead, the purpose of this subgroup analysis is to evaluate the efficacy of HSCT in the subset of chemosensitive patients within the primary refractory /early relapsed population. Review of this exploratory analysis demonstrated a median EFS of 12.1 months (95% CI: 8.5, NE) with a 1-year EFS of 51% (95% CI : 38, 64). The KM curve of EFS is demonstrated below:

Figure 12. FDA - KM Plot of EFS for Subjects that Underwent HSCT



Source: FDA statistical reviewer

Table 25. FDA - Efficacy Outcome of Subjects Who Underwent HSCT (n=62)

Parameter	EFS	PFS	DOR
Median (95% CI)	12.1 mo (8.5, NE)	NR (8.9, NE)	NR (8.9, NE)
Event-free rate, % (95% CI)			
3 month	97% (87, 99)	98% (88, 100)	91% (80, 96)
6 month	74% (61, 84)	84% (71, 91)	76% (61, 85)
9 month	55% (41, 67)	64% (49, 75)	63% (48, 75)
12 month	52% (38, 64)	60% (45, 72)	61% (46, 73)
15 month	50% (36, 62)	60% (45, 72)	61% (46, 73)
18 month	50% (36, 62)	60% (45, 72)	58% (43, 71)

Source: FDA statistical reviewer

Reviewer comment:
Subjects in ZUMA-7 were randomized upfront to the two treatment arms. Bridging therapy in the axicabtagene ciloleucel arm was limited to corticosteroids. Therefore, ZUMA-7 was not designed to determine chemosensitivity of the study participants prior to treatment and the comparative efficacy of axicabtagene ciloleucel in patients with first chemosensitive relapse remains uncertain. Furthermore, even in this high-risk disease setting, one-third of the subjects

randomized to the SOC arm responded to chemotherapy and underwent HSCT. The exploratory analysis outlined above indicates that in this selected subgroup of subjects (n=62) with chemosensitive disease, the outcome with median EFS of 12 months (95% CI: 8.5, NE) and 1-year EFS of 52% (95% CI: 38, 64) is at least comparable to the historical data for HSCT in the second-line setting (Refer to Table-2 in Section 2.2).

In summary, the efficacy of axicabtagene ciloleucel compared to HSCT has not been established in patients with first chemosensitive relapse of large B-cell lymphoma. The results of this post-hoc exploratory analysis indicates that HSCT continues to be a justifiable treatment strategy in refractory and early relapsed LBCL with chemosensitive disease.

8.1.2. Integrated Review of Effectiveness

The Applicant's Position:

The varying study designs and differences in primary endpoint in this pivotal ZUMA-7 study compared with the supporting studies does not allow for an integrated efficacy assessment.

The FDA's Assessment:

FDA agrees with this assessment.

8.1.3. Assessment of Efficacy Across Trials

The Applicant's Position:

This sBLA is based on efficacy results from ZUMA-7 only; thus, this section is not applicable.

The FDA's Assessment:

FDA agrees with this assessment.

8.1.4. Integrated Assessment of Effectiveness

The Applicant's Position:

The varying study designs and differences in primary endpoint in this pivotal ZUMA-7 study compared with the supporting studies does not allow for an integrated efficacy assessment.

The FDA's Assessment:

Clinical benefit was established in ZUMA-7, a Phase 3, randomized, open label trial of second-line therapy of LBCL, that randomized 359 subjects in a 1:1 ratio to either a single infusion of axicabtagene ciloleucel (preceded by lymphodepleting chemotherapy) or to standard therapy. All subjects had either primary refractory disease or relapse within 12 months of completing first-line therapy, were potentially eligible for autologous HSCT, and had not yet received

second-line treatment. Standard therapy consisted of protocol defined, platinum-based chemoimmunotherapy for 2-3 cycles followed by high-dose therapy (HDT) and autologous HSCT in responders (CR or PR).

The primary endpoint was EFS per blinded independent review committee (IRC). Key secondary endpoints were ORR per IRC and overall survival (OS). Overall, 74% of the study population had primary refractory disease, 26% had early relapsed disease; leading diagnoses were de novo DLBCL (63%), high grade B-cell lymphoma (HBCL) (19%) and transformed FL (13%).

A total of 179 subjects were randomized to the SOC arm out of which 168 subjects (94%) received any protocol specified chemoimmunotherapy; 54% (90 out of 168) of the subjects that received any protocol specified therapy responded per central assessment with a CR rate of 35%. Thirty seven percent (62 out of 168) of the treated subjects underwent HSCT. The reasons for not proceeding with HSCT include lack of response to therapy, disease progression, AEs and failure of stem cell mobilization. 180 subjects were randomized to the axicabtagene ciloleucel arm and 170 subjects (94%) received axicabtagene ciloleucel. The reasons for not receiving axicabtagene ciloleucel include study ineligibility, death, PD and AE to lymphodepleting chemotherapy. ORR per central assessment in the axicabtagene ciloleucel treated subjects was 88% (149/170) with CR rate of 68%.

Compared to the SOC arm in which only 35% of the randomized subjects underwent transplantation, 94% of the randomized subjects in the axicabtagene ciloleucel arm underwent definitive treatment with CAR T cell infusion. The main reason that subjects randomized to the SOC arm did not proceed with HSCT was lack of response to chemotherapy. This difference in the proportion of the subjects receiving definitive therapy in the two arms is due to the single dose administration in the CAR T arm and the primarily chemo refractory nature of the study population.

EFS was significantly improved for axicabtagene ciloleucel arm compared to the SOC arm with a stratified HR of 0.40 (95% CI:0.31, 0.51) and a p- value <0.0001. The median EFS in the axicabtagene ciloleucel arm was 8.3 mo (95% CI: 4.5, 15.8 mo) compared to 2 mo (95% CI: 1.6, 2.8 mo) in the SOC arm. The estimated 18-month EFS was 41.5% (95% CI: 34.2, 48.6) vs. 17% (95% CI: 11.8, 23) in SOC arm respectively.

The most common EFS event in both the axicabtagene ciloleucel arm and SOC arm was disease progression (46% and 42%). The key EFS event that is driving the difference between the two arms is the use of new anti-lymphoma therapy (NALT): 6% (11) in the axicabtagene ciloleucel arm and 35% (63) in the SOC arm.

The relatively high rate of NALT resulting in EFS events in the SOC arm compared to the axicabtagene ciloleucel arm was a result of 1) higher rate of discordant response assessment between the IRC and investigators in the SOC arm compared to axicabtagene ciloleucel arm. As a result of the discordant assessment, subjects deemed to be in CR or PR without disease

progression per IRC assessment were determined to be either non-responders or as having disease progression per investigator assessment resulting in administration of NALT. 2) higher proportion of subjects with best response of stable disease in the SOC arm compared to axicabtagene ciloleucel arm prompting the use of NALT and 3) higher rate of randomized subjects who did not receive any protocol specified therapy followed by NALT in the SOC arm. The improvement in EFS was maintained in a sensitivity analysis that excluded 33 such events due to administration of NALT. Substantially more subjects were censored in the axicabtagene ciloleucel arm for ongoing response compared to the SOC arm (40% and 16%). Overall, the improvement in EFS observed in ZUMA-7 is considered clinically meaningful and robust.

The IRC-assessed overall response rate was higher at 83% (95% CI: 77, 89) in the axicabtagene ciloleucel arm compared to 50% (95% CI: 43, 58) in SOC arm (p-value of <0.0001). This difference in ORR was driven primarily by a higher CR rate of 65% (95% CI:58,72) in the axicabtagene ciloleucel arm compared to CR rate of 32% (95% CI:26, 40) in the SOC arm. The median PFS also favored the axicabtagene ciloleucel arm (14.9 mo; 95% CI: 7.2, NE) compared to the SOC arm (5 mo; 95% CI: 3.4, 8.5). An interim OS analysis performed at 75% information level, was not statistically significant. OS tended to favor axicabtagene ciloleucel, with a HR of 0.71 (99.1% CI: 0.46, 1.1), p<0.03 (p-value boundary, 0.008).

Subjects in ZUMA-7 were randomized upfront to the two treatment arms. Bridging therapy in the axicabtagene ciloleucel arm was limited to corticosteroids. Therefore, ZUMA-7 study design was limited in that it was not designed to evaluate the superiority of axicabtagene ciloleucel compared to HSCT in subjects with chemosensitive relapse who were able to undergo transplantation. Hence comparative efficacy of axicabtagene ciloleucel in patients with first chemosensitive relapse remains uncertain. Furthermore, even in this high-risk disease setting, one-third of the subjects randomized to the SOC arm responded to chemotherapy and underwent HSCT. An exploratory analysis performed in these 62 subjects in the SOC arm with chemosensitive disease that underwent HSCT indicates a median EFS of 12 months (95% CI: 8.5, NE) and 1-year EFS of 52% (95% CI: 38, 64) which is at least comparable to the historical data for HSCT in the second-line setting. Therefore, the efficacy of axicabtagene ciloleucel compared to HSCT has not been established in patients with first chemo-sensitive relapse of large B-cell lymphoma. HSCT continues to be a justifiable treatment strategy in refractory and early relapsed LBCL with chemosensitive disease. A retrospective CIBMTR analysis was recently published,[7] evaluating outcomes with autologous HSCT vs. CAR-T therapy for first relapse of DLBCL in patients with a best response of PR after second-line chemotherapy. In patients with ≤ 2 prior lines of therapy, there was no difference in PFS or OS between the groups; however, the analysis has multiple limitations, including imbalance in extent of prior therapy.

In summary, ZUMA-7 provides substantial evidence of efficacy of axicabtagene ciloleucel compared to standard therapy in patients with primary refractory and early relapsed LBCL based on consistent improvement in EFS ,PFS, ORR, CR and supported by OS.

The magnitude of clinical benefit observed with axicabtagene ciloleucel is the basis for recommended regular approval. Because the study enrolled patients with primary refractory

and early relapsed LBCL (within 1 year of first-line chemoimmunotherapy), the recommended indication is restricted to adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first- line chemoimmunotherapy. Since management of r/r primary mediastinal B-cell lymphoma is similar to other r/r LBCLs and given that axicabtagene ciloleucel is approved for the management of PMBCL after two or more prior lines of therapy, the review team did not restrict the indication statement in this regard. As with the currently approved LBCL indication, the new indication statement includes other LBCL subtypes with few or no data, but which generally share similar treatment paradigms in the r/r setting and have a high unmet need. Given that patients with primary CNS lymphoma were ineligible for ZUMA-7, there are no clinical data addressing the efficacy and safety axicabtagene ciloleucel in this population. In addition, there are concerns about the potential for adverse outcomes if neurotoxicity were to develop in patients with pre-existent increased intracranial pressure and/or space occupying mass lesions within the brain. Therefore, the indication statement will have a LOU that axicabtagene ciloleucel is not indicated for the treatment of patients with primary CNS lymphoma. This is the same LOU statement in place for the current indication statement for axicabtagene ciloleucel for r/r LBCL after two or more lines of systemic therapy.

8.2. Review of Safety

The Applicant's Position:

The primary evaluation of the safety of second-line axicabtagene ciloleucel presented in this SCS is based on ZUMA-7. This Phase 3, randomized, open-label study evaluated the efficacy and safety of axicabtagene ciloleucel versus SOCT in subjects with r/r LBCL. Specifically, subjects in ZUMA-7 were those with LBCL who had received first-line rituximab and anthracycline-based chemotherapy and had either primary refractory disease or had relapsed within 12 months of their first-line treatment. A total of 359 subjects were enrolled (180 in the axicabtagene ciloleucel arm and 179 in the SOCT arm) and 338 subjects were evaluated for safety (170 received axicabtagene ciloleucel and 168 received ≥ 1 dose of SOCT). By the date of data cutoff for the analysis presented in this SCS (18 March 2021), subjects in ZUMA-7 have had the opportunity to be followed-up for ≥ 15 months after their infusion of axicabtagene ciloleucel or their first dose of standard of care salvage chemotherapy.

In ZUMA-7, TEAEs were generally manageable and consistent with the known effects of axicabtagene ciloleucel and SOCT, with no new safety signals observed in either treatment arm.

Across all subjects with r/r LBCL, 50% of subjects in the axicabtagene ciloleucel arm experienced SAEs and 42% experienced Grade 3 or higher SAEs compared with 46% and 40% in the SOCT arm. Worst Grade 3 or higher TEAEs occurred in 91% and 83% of subjects in the axicabtagene ciloleucel and SOCT arms, respectively, and worst Grade 3 or higher treatment related TEAEs were numerically lower in the axicabtagene ciloleucel arm compared with the SOCT arm (66% and 78%, respectively). Fatal TEAEs in both treatment arms were numerically low and were reported for 7 subjects in the axicabtagene ciloleucel arm and 2 subjects in the SOCT arm, including 1 event (hepatitis B reactivation) deemed related to axicabtagene ciloleucel and 2 events (acute respiratory distress and cardiac arrest) deemed related to HDT.

Subject incidences of the known axicabtagene ciloleucel risks of neurologic events, infections, and hypogammaglobulinemia were higher with axicabtagene ciloleucel treatment compared with SOCT (neurologic events: 60% versus 20%; infections: 41% versus 30%; hypogammaglobulinemia: 11% versus 1%, respectively). Cytopenias are a known risk of both axicabtagene ciloleucel and chemotherapy, and the subject incidence of cytopenias was the same between treatment arms (80% each). Differences were observed between treatment arms for individual cytopenias, and as investigators recorded fever separately from neutropenia if the fever was attributed to CRS, the reported subject incidences of neutropenia and febrile neutropenia differed between the axicabtagene ciloleucel and SOCT arms (neutropenia: 72% and 55%, respectively; febrile neutropenia: 2% and 27%, respectively). Subject incidences of prolonged cytopenias (ie, present on or after Therapy day 30 after the first dose of study treatment) were lower with axicabtagene ciloleucel treatment than SOCT overall (41% versus 70%, respectively) and for prolonged thrombocytopenia (19% versus 51%, respectively) and anemia (14% versus 50%, respectively). In the axicabtagene ciloleucel arm, Grade 3 or higher

CRS and neurologic events were reported in 6% and 21% of subjects, respectively, manageable with medical intervention and generally resolved.

Supporting evidence for the safety of axicabtagene ciloleucel is provided by ZUMA-1, and the pooled axicabtagene ciloleucel population of ZUMA-7 and ZUMA-1. These studies are summarized in Table 4. The FDA and EC approvals of axicabtagene ciloleucel were based on the results of ZUMA-1; a single-arm, multicenter study in adult subjects with refractory aggressive LBCL. At the time of the original submission, ZUMA-1 comprised 2 phases: Phase 1 and Phase 2 Cohorts 1 and 2. While the scope of the ZUMA-1 study has increased since the original submission, safety data presented in the summary of clinical safety are from the 108 subjects treated with axicabtagene ciloleucel in Phase 1 and Phase 2 Cohorts 1 and 2. For ease of reference in this SCS, ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2 are hereafter referred to as ZUMA-1. By the date of data cutoff, all subjects in ZUMA-1 have had the opportunity to be followed-up for ≥ 54 months after their infusion of axicabtagene ciloleucel (based on a data cutoff date of 18 March 2021).

The purpose of pooling safety data from the axicabtagene ciloleucel arm of ZUMA-7 and from ZUMA-1 is to provide a larger dataset of axicabtagene ciloleucel-treated subjects in order to evaluate the safety profile of axicabtagene ciloleucel when administered across various lines of therapy, and also to compare its safety profile with that of SOCT. The pooled population comprises 278 subjects with LBCL who were treated with axicabtagene ciloleucel in ZUMA-7 and ZUMA-1. A summary of the pooled safety results is provided in Section 8.2.11.

The overall safety profile of axicabtagene ciloleucel demonstrated in ZUMA-7 and in the pooled analysis of ZUMA-7 and ZUMA-1 safety data supports use of axicabtagene ciloleucel as a therapeutic option for the second line treatment of r/r LBCL.

The FDA's Assessment:

The clinical safety review was primarily based on analysis of data submitted for the 168 subjects treated with conforming axicabtagene ciloleucel in ZUMA-7. Data reviewed included datasets, clinical study report, summary of clinical safety, subject narratives, several IRs and data in the public domain. JMP 14 (SAS Institute Inc.) was used to reproduce safety analyses based on the submitted safety datasets and to conduct additional exploratory analyses. The primary safety review was based on the originally submitted data with a cut-off date of March 18, 2021. The database lock for the 120-day safety update report (SUR) was August 26, 2021. Key findings in the safety update report (SUR) are provided in Section 8.2.9.

Additional supportive safety data was reviewed for study of axicabtagene ciloleucel in r/r LBCL after 2 or more lines of therapy (ZUMA-1).

8.2.1. **Safety Review Approach**

The Applicant's Position:

In ZUMA-7, investigators were to report all AEs that occurred from enrollment (ie,

randomization) through the Study Day 150 visit or until a change in the subject's lymphoma therapy, whichever occurred first. Targeted SAEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) were to be monitored and reported for up to 5 or 15 years for SOCT or axicabtagene ciloleucel treatment arms, respectively, or until disease progression, whichever occurred first.

TEAEs were defined as any AE with onset on or after the axicabtagene ciloleucel infusion for the axicabtagene ciloleucel arm, and as any AE with onset on or after the first dose of salvage chemotherapy for the SOCT arm. TEAEs of special interest for axicabtagene ciloleucel treatment included important identified risks (CRS, neurologic events [including cerebral edema], cytopenias [thrombocytopenia, neutropenia, and anemia], infections, and hypogammaglobulinemia) and important potential risks (secondary malignancies, immunogenicity, replication-competent retrovirus [RCR], tumor lysis syndrome, and aggravation of graft-versus-host-disease [GVHD]).

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1, and the severity of AEs other than CRS was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

CRS is induced by activated anti-CD19 CAR T-cells upon engagement with the CD19 target. Therefore, all reported events of CRS were generally considered to be related to axicabtagene ciloleucel treatment. CRS was graded as a syndrome according to a modification of the criteria established by Lee and colleagues {Lee 2014} that did not include neurologic AEs as part of CRS unless marked by the investigator as a symptom of CRS. The severity of individual signs/symptoms of CRS were graded per CTCAE version 4.03.

Neurologic events were identified separately from CRS based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. The search strategy focused on CNS toxicity without regard to relatedness, temporal relationship, or concomitant conditions and also identified via the system organ class search strategy (MedDRA search terms list that identifies neurologic events based on the MedDRA system organ classes of psychiatric disorders and nervous system disorders).

The FDA's Assessment:

1. For subjects who were enrolled but did not receive axicabtagene ciloleucel, the AE reporting period ended 30 days after the last procedure such as leukapheresis and conditioning chemotherapy.

2. After the Day 150 post-randomization visit, only targeted SAEs were reported. SAEs which the investigator assessed as related to axicabtagene ciloleucel were to be reported regardless of the time period.

3. For the purpose of this safety review, study day 0 is defined as the day of randomization and treatment day 0 is defined as the day of the first axicabtagene ciloleucel infusion in the axicabtagene ciloleucel arm or the day of first chemoimmunotherapy infusion in the SOC arm.

4. Because CAR T cell therapy is preceded by conditioning chemotherapy, it is often difficult to parse out the causality of AEs. Therefore, adverse drug reactions (ADRs) were defined as any TEAE occurring after the start of axicabtagene ciloleucel infusion regardless of perceived relationship and causality with the investigational product. A separate analysis of AEs that occurred from leukapheresis until the start of conditioning chemotherapy, and from the start of conditioning regimen until the day before axicabtagene ciloleucel infusion are conducted and presented separately.

5. The Applicant reported AEs by preferred terms which may underestimate the incidence of some AEs. To minimize underestimation of AEs, FDA grouped preferred terms that represent the same disease process. The reviewer utilized a grouping strategy for comprehensive analyses of AEs that is consistent with the grouping practices for review of similar agents within this class of therapies and with previous licensing trials of axicabtagene ciloleucel: ZUMA-1 and ZUMA-5. The complete list of FDA grouped terms for all TEAEs is presented in Section 18.4, APPENDIX .

6. The Applicant's definition of TEAE defined as any AE with onset on or after the axicabtagene ciloleucel infusion for the axicabtagene ciloleucel arm, and as any AE with onset on or after the first dose of salvage chemotherapy for the SOC arm is acceptable.

7. In general, all grade AEs were counted by maximum toxicity (max. tox) grade (i.e., multiple incidences of the same AE in one subject are counted once at the worst grade for this subject).

8. FDA's assessment of neurologic toxicity is the system organ class (SOC) strategy which includes neurologic events based on the SOC of psychiatric and nervous system disorders. Some of the neuropsychiatric AEs that were isolated and non-specific such as insomnia or anxiety were not included under NT analysis. In addition, other preferred terms that indicate neurotoxicity but were misclassified under other system organ classes (such as muscular weakness under Musculoskeletal and Connective Tissue Disorders and gait disturbance under General Disorders) are also included. For details, refer to Section 8.2.5 under Neurotoxicity.

6. The Applicant's method for CRS grading {Lee 2014} did not include neurologic AEs as part of CRS unless marked by the investigator as a symptom of CRS. This methodology is consistent with that of ZUMA-1 and ZUMA-5 studies and is appropriate.

7. Applicant defined the safety analysis set as the subset of all randomized subjects who received at least 1 dose of axicabtagene ciloleucel (n=170) or SOC chemotherapy (n=168). We excluded two subjects who received non-conformal axicabtagene ciloleucel (USUBJID: (b) (6) and (b) (6)) from the safety analysis set. Therefore, the safety analysis set in the axicabtagene ciloleucel and SOC arm each included 168 subjects.

8. Safety analysis of the retreatment period (with second dose of axicabtagene ciloleucel) is outside the scope of this BLA review.

Reviewer comment:
The review team considers a comparative toxicity analysis between the two study arms of limited utility for the following reasons:

1. The two treatment arms have fundamentally different treatment modalities that have distinct toxicity profile rendering a comparative toxicity analysis uninformative. In the axicabtagene ciloleucel arm, subjects underwent leukapheresis, received lymphodepleting chemotherapy (LD) followed by axicabtagene ciloleucel. The SOC arm incorporated platinum-based chemoimmunotherapy followed by HDT/HSCT in responders. Toxicities such as CRS and neurologic toxicity are anticipated toxicities of the axicabtagene ciloleucel arm and not expected with the SOC arm. Similarly, toxicities such as mucositis, emesis and peripheral neuropathy are expected toxicities of the SOC arm. Given the innate differences in toxicity between these two treatment arms, comparison of toxicity would imply a comparative safety claim that is misleading.

In general, comparative toxicity analysis is useful in studies that compare either two different chemoimmunotherapy regimens or compare SOC with SOC in combination with an additional therapy (add-on trial).

2. Significant heterogeneity in the SOC arm in terms of treatment exposure:
While 100% of the safety population in the axicabtagene ciloleucel arm received definitive therapy including LD and axicabtagene ciloleucel in ZUMA-7 , the safety population in the SOC arm is significantly heterogenous. Out of the 168 subjects in the safety population, 10% received 1 cycle of chemotherapy, 54% received 2 cycles of chemotherapy, 36% received 3 cycles of chemotherapy and 37% subjects received 2-3 cycles of chemotherapy followed by HDT and HSCT. Therefore, toxicities reported for the SOC arm is not reflective of the intended treatment plan and are likely significantly diminished. Therefore, the safety data from the SOC arm is considered inadequate for comparison of toxicity rates between the two arms.

3. Given that the safety of chemoimmunotherapy followed by HDT and HSCT (SOC arm) is well established , the safety analysis in this review focusses on the results of axicabtagene ciloleucel arm.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

In ZUMA-7, of the 170 subjects in the axicabtagene ciloleucel arm of the SAS, 169 subjects had available body surface area (BSA)-adjusted dose information, for whom the median total BSA-adjusted dose of cyclophosphamide was 1,500 mg/m^2 (range: 1,211 to 1,618 mg/m^2) and of fludarabine was 90 mg/m^2 (range: 60 to 96 mg/m^2). A total of 165 and 164 subjects received the planned total BSA-adjusted dose (± 10%) of cyclophosphamide (1,500 mg/m^2) and

fludarabine (90 mg/m^2), respectively.

In the axicabtagene ciloleucel arm of the SAS, 166 subjects (98%) received within 10% of the planned dose of 2 × 10^6 anti-CD19 CAR T cells/kg (or a flat dose of 200 × 10^6 anti-CD19 CAR T-cells for subjects weighing > 100 kg). For the 137 subjects who received axicabtagene ciloleucel and weighed ≤ 100 kg, the median weight-adjusted dose was 2 × 10^6 anti-CD19 CAR T cells/kg (range: 1.0 to 2.1 × 10^6 cells/kg) and all 33 subjects who weighed > 100 kg received the planned flat total dose of 200 × 10^6 anti-CD19 CAR T cells. For all 170 subjects in the axicabtagene ciloleucel arm of the SAS, the median total number of anti-CD19 CAR T-cells in the axicabtagene ciloleucel infusion was 170 × 10^6 cells (range: 58 to 200 × 10^6 cells) and the median total number of T cells infused was 301.5 × 10^6 (range: 88 to 633 × 10^6 cells).

For the 168 subjects in the SOCT arm of the SAS, 152 subjects (90%) received 2 or 3 cycles as directed by the protocol, and 16 subjects (10%) received 1 cycle of salvage chemotherapy. Among the subjects who received 2 or 3 cycles of salvage chemotherapy and had a CR or PR, 62 subjects (37% of the SOCT − SAS) went on to receive HDT-auto-SCT and 3 subjects (2% of the SOCT − SAS), excluding disease progression or those who initiated HDT but did not complete auto-SCT, did not (1 subject was considered to have an insufficient response by the investigator, 1 subject had a PR before Study Day 50 and PD at Study Day 50, and 1 subject had a TEAE of blood stem cell harvest failure).

The FDA's Assessment:

Axicabtagene ciloleucel arm:
Out of the safety population of 168 subjects, BSA adjusted dose of cyclophosphamide and fludarabine is available in 167 subjects.

For cyclophosphamide, the total administered dose ranged from 1211 mg/m2 to 1618 mg/m2 with median dose of 1500 mg/m2. Majority of the subjects (98%) received within 10% of the protocol specified dose except for 4 subjects that received total dose of 1211-1337 mg/m2 which was less than 90% of the protocol specified dose.

For fludarabine, the total administered dose ranged from 60 mg/m2 to 96mg/m2 with median dose of 90 mg/m2. Majority of the subjects received (97%) within 10% of the protocol specified dose except for 5 subjects that received a total dose of 60-80 mg/m2 which was less than 90% of the protocol specified dose.

Out of the safety population of 168 subjects, 33 subjects weighed >100 kg. All of these subjects received the protocol specified dose of 200 x10e6 CAR+ T cells. For the remainder of the 135 subjects, the dose of axicabtagene ciloleucel that was administered ranged from 1-2.1 x10e6 CAR+ T cells/kg with a median dose of 2x10e6 CAR+T cells/kg. Seven subjects (4%) received 2.1 x10e6 CAR+ T cells/kg and three subjects (2%) received dose of 1-1.6 x10e6 CAR+ T cells/kg. Overall, 94% of the subjects in the axicabtagene ciloleucel arm received protocol specified dose.

SOC arm: FDA agrees with the Applicant's assessment.

Reviewer comment:
Overall, the exposure to LD and axicabtagene ciloleucel was within the target planned in the protocol and is adequate to support characterization of the safety profile of axicabtagene ciloleucel in the intended population.

Relevant characteristics of the safety population:

The Applicant's Position:

Study populations included in the safety analysis of axicabtagene ciloleucel are summarized in Table 4. The ZUMA-7 study population consisted of 359 subjects with r/r LBCL who were refractory to or relapsed within a year of first-line immunochemotherapy and included a high percentage of subjects with high-risk features and known poor prognosis to standard chemotherapy-based therapy, including inadequate response to first-line chemoimmunotherapy (refractory or early relapse), diagnosis of HGBL, advanced disease stage, extranodal disease, and older age. Of the 359 subjects, 180 were randomized to the axicabtagene ciloleucel arm and 179 subjects were randomized to the SOCT arm.

The FDA's Assessment:
As stated earlier, FDA's safety analysis set (SAS) included all subjects who received at least one dose of the SOC chemotherapy (n=168) and all subjects who received conformal axicabtagene ciloleucel (n=168). Two subjects that received non-conformal product were excluded from the safety analysis set in the axicabtagene ciloleucel arm.

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

The Applicant's Position: Other baseline characteristics have been described in Section 8.1.2.

The FDA's Assessment:
Axicabtagene ciloleucel Arm:
Overall, the median age was 59 years (range: 21 to 80 years), and 49 subjects (29%) were ≥ 65 years of age. One hundred and four subjects (62%) were male, and the majority were white (137 subjects, 82%); 72% of the subjects were treated in the US; 73% of the subjects were primary refractory; and 27% had relapsed within 1 year of front-line therapy.

Table 26. FDA - Demographic and Baseline Characteristics of the Safety Population (Axicabtagene Ciloleucel)

Demographic Group	Analysis population N=168
Age	
<65 years	119 (71%)
≥65 years	49 (29%)
Mean (SD)	57 (12)
Median (Range)	59 (21, 80)
Sex	
Total	168
Male	104 (62%)
Female	64 (38%)
Race	
Total	168
White	137 (82%)
Black or African American	9 (5%)
Asian	10 (6%)
Native Hawaiian or other Pacific Islander	2 (1%)
Other	10 (6%)
Ethnicity	
Total	168
Hispanic or Latino	8 (5%)
Non-Hispanic or Latino	157 (93%)
Not reported	3 (2%)
Country	
Total	168
United States	121 (72%)
Non-US	47 (28%)
Response to first-line therapy at randomization	
Total	168
Primary refractory	122 (73%)
Relapsed within 1 year of front-line therapy	46 (27%)
ECOG performance status at baseline	168
Performance status 0	91 (54%)
Performance status 1	77 (46%)

Source: FDA analysis of ADSL.xpt

Adequacy of the safety database:

The Applicant's Position:

The safety profile of axicabtagene ciloleucel is well-characterized. As of 17 April 2021, 808 subjects have been exposed to axicabtagene ciloleucel in company-sponsored interventional clinical studies. It is estimated that 4,497 patients have been exposed to axicabtagene ciloleucel in post authorization use.

The size of the safety database for ZUMA-7 (N=338), supported by supplemental data from the ZUMA-1 (N=108), is considered adequate to support the benefit-risk assessment for the use of axicabtagene ciloleucel in patients with r/r LBCL and adequately represents the target patient population.

The FDA's Assessment:
The reviewer agrees that the safety database is considered adequate to identify most common AEs, support the benefit-risk assessment, and represent the target patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to safety data integrity or quality were identified for ZUMA-7.

The FDA's Assessment:
Safety analysis is based on FDA's adjudication of AEs. Please refer to FDA's assessment under Data Quality and Integrity on Page 83.

Categorization of Adverse Event

The Applicant's Position:

Unless noted otherwise, AEs of special interest are collected for both treatment arms.

A description of the safety review approach is presented in Section 8.2.1.

The FDA's Assessment:
See FDA assessment Section under Section 8.2.1.

Routine Clinical Tests

The Applicant's Position:

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, ECGs, and physical examinations. Specialty tests were conducted for RCR and antibodies to axicabtagene ciloleucel. Additional information is provided in m5.2.5.2, ZUMA-7 Primary Analysis CSR, Section 7.5.5. The Schedules of Assessments are provided in m5.2.5.2, ZUMA-7 Primary Analysis CSR, Section 7.5.1.

The FDA's Assessment:
See schedule of assessments in Table 60,Table 61 and Table 62 in Appendix. Overall, the schedule of testing in ZUMA-7 is considered adequate for the assessment of safety.

8.2.4. Safety Results

Deaths

The Applicant's Position:

Of the 338 subjects in the SAS in ZUMA-7, 64 subjects (38%) in the axicabtagene ciloleucel arm and 78 subjects (46%) in the SOCT arm had died. Of the 64 subjects in the axicabtagene ciloleucel arm who died, 6 died more than 30 days but less than 3 months from the axicabtagene ciloleucel infusion, and 58 died more than 3 months after the axicabtagene ciloleucel infusion. Of the 78 subjects in the SOCT arm who died, 3 died more than 30 days but less than 3 months after the first dose of salvage chemotherapy, and 75 died more than 3 months after the first dose of salvage chemotherapy.

Among subjects in the SAS, 6 subjects in the axicabtagene ciloleucel arm and 2 subjects in the SOCT arm died due to TEAEs; among these, the deaths of 2 subjects in each treatment arm were considered to be related to study treatment. Additional information is provided in m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 11.3.

The FDA's Assessment:
The tables below summarize all deaths in the safety population of both arms using a March 18, 2021 data cut-off date (data cut-off date for the primary analysis).

Table 27. FDA - Deaths in Safety Population of ZUMA-7

Parameter	Axicabtagene ciloleucel N=168 n (%)	Standard of Care N=168 n (%)
All Deaths	63 (38%)	82 (49%)
Progressive Disease	47 (28%)	64 (38%)
Fatal adverse events	3 (2%)	2 (1%)
Fatal AEs ≤30 days of treatment start day	0	0
Fatal AE between 30 days to 3 months of treatment start day	0	0
Fatal AE >3 months from treatment start day	3	2
Other causes (unrelated AEs)	12 (7%)	9 (5%)
Unknown cause	1 (0.6%)	7* (4%)

*Includes the four deaths in SOC that were discovered from public sources after BLA submission
Source: FDA analysis of ADSL and ADAEFDA datasets and safety narratives

Table 28. FDA - Summary of Fatal AEs Observed in Axicabtagene Ciloleucel Arm (N=168)

USUBJID	Fatal AE	Therapy Day of Death	PD	NALT
(b) (6)	Progressive multifocal leukoencephalopathy	207	No	No
	Sepsis	442	No	No
	Encephalopathy	846	No	No

Table 29. FDA - Summary of Fatal AEs Observed in SOC Arm (N=168)

USUBJID	Fatal AE*	Therapy day of death/ Day post HSCT ^	PD	NALT
(b) (6)	Ischemic stroke cardiac arrest	146 / 75	No	No
	PJP pneumonia, ARDS	161/ 48	No	No

*Both deaths occurred in the post-transplant setting
^ Calculated as death day – transplant day + 1

Table 30. FDA - Deaths from Unrelated AEs and Unknown Cause in the Axicabtagene Ciloleucel Arm (N=168)

USUBJID	Cause of Death	Therapy Day of Death	Reviewer Comment
(b) (6)	Myocardial infarction	53	Subject was in remission and did not receive any subsequent therapy
	Stroke	122	Subject developed PD on day 72 Subsequent therapy: RGDP x 2 cycles from Days 87-122 with PD
	COVID 19	275	Subject did not have PD and did not receive any subsequent therapy.
	COVID 19	278	Subject did not have PD and did not receive any subsequent therapy.
	Euthanasia due to progressive disease	321	Subject developed PD on Day 70 Subsequent therapy: R-DHAP x 3 followed by HSCT on Day 181 with best response of PD.
	Respiratory failure	332	Subject developed PD on Day 30 Subsequent therapy: Radiation therapy from Days 46-71 followed by PD.
	Septic shock	378	Subject developed PD on Day 259

USUBJID	Cause of Death	Therapy Day of Death	Reviewer Comment
			Subsequent therapy: R-GDP x 2 cycles followed by allogeneic SCT on Day 374.
(b) (6)	Pulmonary infection	417	Subject developed PD on Day 36 Subsequent therapy: R-DHAP X3: Day 39-79 Polatuzumab +BR: Day 112-196 Allogeneic SCT: Day 227 with best response of CR.
	C difficile and ischemic colitis	422	Subject developed PD on Day 70 Subsequent therapy: Nivolumab+varlilumab x1: Day 91 R-DHAP X 1 cycle: Day 103-106 R-DHAX 1 cycle: Day 126-128 R-lenalidomide x 5 cycles: Day 153-305 R-ICE X 2 cycles: Day 306-336 with best response of PR
	Lung adenocarcinoma	517	Subject was a smoker, diagnosed with lung adenocarcinoma; Stage IIIB (pleural involvement) on Day 456. Subject was treated with systemic chemoimmunotherapy on Day 464. Subject died from lung adenocarcinoma. No PD or subsequent therapy.
	Unknown cause	525	Pt had PD on day 72. Subsequent therapy: R-DHAX X 1 cycle: Day 85-86 R-ICE X 3 cycles: Day 109-151 EED inhibitor: Day 183 Polatuzumab+ BR x 1 cycle: Day 244 R-CVP and procarbazine x 5 cycles: Day 244-400 with best response of PR.
	COVID 19	651	Subject developed PD on Day 76. Subsequent therapy:

USUBJID	Cause of Death	Therapy Day of Death	Reviewer Comment
			Pembro+len+rituximab: Day 118-180 Polatuzumab+ BR: 3 cycles, Day 197-251 Allogeneic SCT: Day 288 with best response of CR.
(b) (6)	COVID 19	696	Subject had PD on Day 87. Subsequent therapy: Nivolumab+varlilumab x6 cycles: Day 125-279 Auto-HSCT: Day 330 with best response of CR.

Table 31. FDA - Deaths from Unrelated AEs and Unknown Cause in the SOC Arm (N=168)

USUBJID	Cause of Death	Therapy Day of Death /Day post-transplant	HSCT Y/N/ Treatment Day	Reviewer comment
(b) (6)	Urosepsis	233	No	Subject had SD on Day 50 followed by PD. Subsequent therapy: steroids and then yescarta on Day 126 with best response of CR.
	Hyperinflammation	275	No	Subject had PD on Day 50 . Subsequent therapy: XRT and yescarta from Day 83-104 with best response of NE.
	Sepsis	295	No	Subject had PD on Day 46. Subsequent therapy: yescarta on Day 83 with best response of PR.
	Sepsis	396 Post-transplant: Day: 313	Yes on Day 84	Subject had PD on Day 259. Subsequent therapy: steroids and cytoxan from Day 356-374 with best response of NE.
	COVID 19	499	No	Subject had SD on Day 50. Subsequent therapy:

USUBJID	Cause of Death	Therapy Day of Death /Day post-transplant	HSCT Y/N/ Treatment Day	Reviewer comment
				tisagenlecleucel on Day 153 with best response of CR.
(b) (6)	Subarachnoid hemorrhage, subdural hematoma cardiopulmonary arrest	557 Post-transplant Day: 494	Yes on Day 64	Subject developed PD on Day 216 Subsequent therapy: Polatuzumab with BR on day 234 x 6 cycles with best response of CR followed by PD on Day 529.
	COVID 19	568	No	Subject developed PD on Day 19. Subsequent therapy: Yescarta on Day 77 with best response of PR.
	Septic shock	614	No	Subject developed PD on Day 83 Subsequent therapies: Anti-CD3 /CD20 BITE: Day 218-267 Tisagenlecleucel: Day 336-342 Polatuzumab+BR: Day 492-602 Cytoxan: Day 605-614 with best response of NE
	Cryptogenic organizing pneumonia	1062	No	Stable disease on Day 50. Subsequent therapies: Yescarta and atezolizumab: Day 78-147 Anti-CD20 bispecific AB RGN-1979: Day 579-637 Allogeneic stem cell transplant: Day 671 Polatuzumab+BR:Day 698-761 Allogeneic SCT: Day 799 with best response of PR
	Unknown	306	No	Subject had PD on Day 40. Subsequent therapies: Brentuximab-CHP:Day 68-89 Gemcitabine+oxaliplatin: Day 125

USUBJID	Cause of Death	Therapy Day of Death /Day post-transplant	HSCT Y/N/ Treatment Day	Reviewer comment
(b) (6)				Yescarta: Day 142-147 Brentuximab : Day 232-233 with best response NE
	Unknown	299	No	Subject had PD on Day 92 . Subsequent therapies: Mini-BEAM: Day 99-154 Yescarta: Day 245 with best response of NE
	Unknown	221	No	Subject had PD on Day 43. Subsequent therapy: Mini-BEAM: Day 52-84 with best response of PD

Therapy day is day from start of therapy. Therapy Day 0 is the day of infusion of Axicabtagene ciloleucel and Cycle 1 Day 1 for the standard of care salvage chemotherapy.

Brief description of all deaths and narratives for subjects who died due to a fatal AE are listed below.

Axicabtagene ciloleucel arm:
Adverse Events:

1. Subject (b) (6), a 61-year-old white male with a 50-pack-year smoking history, COPD, non-small cell lung cancer s/p pneumonectomy in 2016 and recurrent lung infections in 2016-2017 was admitted on treatment day 434 with productive cough and dyspnea. A bronchoscopy revealed polymicrobial infection with E. Coli and invasive aspergillus. He was not neutropenic prior to admission (Day 430: ANC=9000/mm3) with no history of hypogammaglobulinemia. On treatment day 436, subject developed grade 4 sepsis and was treated with broad spectrum antibiotics and anti-fungals. Subject died on treatment day 442 from sepsis and respiratory failure. Subject was in remission at the time of death. While this subject was predisposed to respiratory infections, lymphodepleting chemotherapy followed by axicabtagene ciloleucel is associated with risk of serious and fatal infections. Therefore, this death is considered related to axicabtagene ciloleucel.

2. Subject (b) (6), a 57-year-old white male was admitted to the hospital with impaired short- and long-term memory and confusion on treatment day 176. Diagnostic work up included MRI of the brain performed on treatment day 177 which revealed white matter abnormalities. CSF evaluated on treatment day 178 was positive for JC (John Cunningham) virus. He was diagnosed with grade 4 progressive multifocal leukoencephalopathy (PML) and treated with maraviroc. He died on treatment day 207 from PML. Subject was in remission at the time of death. This death is considered related to conditioning chemotherapy (fludarabine)

and axicabtagene ciloleucel.

3. Subject (b) (6), a 66-year-old white female developed NT on treatment day 6 which resolved on day 21. She was overall doing well until she developed grade 3 staphylococcal pneumonia and Grade 1 CMV infection on treatment day 644-654 .Following recovery from these AEs, she developed failure to thrive, confusion and dizziness. She also developed orthostatic hypotension requiring midodrine and fludrocortisone. She fell on treatment day 759 due to orthostatic hypotension sustaining a laceration. At the time of fall her platelet count was 77,000/mm^3. She underwent head CT scan which revealed a 5-millimeter acute interhemispheric subdural hematoma with no mass effect. She subsequently became increasingly confused with dizziness, weakness and failure to thrive and was hospitalized from treatment day 820-822 for Grade 4 confusion. MRI of the brain done to evaluate confusion showed chronic microangiopathic changes with questionable demyelinating plaques and no evidence of any dominant subdural hematoma. Lumbar puncture was negative for infection. Limited EEG showed generalized slowing. The patient continued to have neurological deterioration and was transferred to hospice where she died on treatment day 846 from encephalopathy. Subject was in remission at the time of death. The death is deemed to be a delayed NT event from axicabtagene ciloleucel.

Reviewer comment:
The Applicant did not report this event as a Grade 5 AE in the original ADAE dataset as it occurred after Day 150 post-randomization and since the investigator did not consider this as a targeted SAE or related to axicabtagene ciloleucel. The review team considered this AE as Grade 5 encephalopathy from axicabtagene ciloleucel and the ADAE dataset was updated to include this AE.

Standard of care arm:
1. Subject ID (b) (6) was a 75-year-old white female who was treated with two cycles of R-GDP. She was subsequently treated with high dose conditioning chemotherapy of BEAM followed by CD34+ stem cell infusion on treatment day 72. She sustained grade 4 ischemic stroke on treatment day 145 and died the following day (treatment day 146) due to cardiac arrest. This death is considered related to HSCT and occurred 75 days post transplantation.

2. Subject ID (b) (6) was 55 years old white female who received 2 cycles of R-GDP followed with high dose conditioning chemotherapy of LEAM followed by CD34+ stem cells on treatment day 114. On treatment day 144 , she developed Grade 4 pneumocystis jirovecii pneumonia and ARDS. She died from ARDS on treatment day 161. This death is considered related to HSCT and occurred 48 days post transplantation.

No deaths occurred within 30 days of treatment in either arm.

Deaths within 3 months of Therapy:
Axicabtagene Ciloleucel Arm: Six subjects died within 3 months of initiating therapy. Five deaths were from disease progression and two out of these five subjects had initiated subsequent

therapy. One death was from AE (myocardial infarction).

SOC Arm: Three subjects died within 3 months of initiating therapy in the SOC arm. None of these subjects underwent HDT/HSCT. All three deaths were from disease progression and two out of the three subjects had initiated subsequent therapy.

Death from unknown cause:
Axicabtagene ciloleucel Arm: One subject in the axicabtagene ciloleucel arm died from unknown cause after PD and receipt of subsequent anti-lymphoma therapy (Please refer to Table 30).

SOC Arm: In the initial submission, three subjects in the SOC arm died from unknown cause. All deaths followed disease progression and receipt of subsequent anti-lymphoma therapy. (Please refer to Table 31).In response to an FDA query, four additional deaths were discovered from public records in subjects who had discontinued from the study. These deaths had occurred prior to the data cut-off date and after disease progression. The cause of death for these four subjects is not known.

None of these seven subjects that died from unknown cause underwent protocol specified HSCT and all seven deaths occurred > 90 days after treatment start day.

Reviewer comment:
1. Subject (b) (6) ,a 60-year-old white male received non-conformal axicabtagene ciloleucel and was excluded from the safety analysis set, died from fulminant hepatic failure due to reactivation of hepatitis B on treatment day 422. This subject had history of hepatitis B which was previously treated with antiviral therapy. At the time of enrollment, he was positive for hepatitis B core antibody and hepatitis B surface antigen but negative for HBV PCR. He was on prophylaxis with entecavir at the time of study enrollment. He subsequently discontinued entecavir and presented on treatment day 399 with grade 3 reactivation of hepatitis B and subsequently died from fulminant hepatic failure. Although this AE occurred in recipient of non-conformal product, this AE is related to the immunosuppression from conditioning chemotherapy and axicabtagene ciloleucel. Therefore, this fatal AE of hepatic failure from reactivation of hepatitis B will be included in the label.

2. Subject (b) (6) a 49-year-old white male with medical history of deep vein thrombosis and pulmonary embolism with onset at the time of lymphoma diagnosis. He was treated with enoxaparin and remained on that until his death. Subject was an active smoker and had family history of heart disease. He had no personal history of hypertension, diabetes or hypercholesterolemia. He died on treatment day 53 from grade 5 myocardial infarction. Subject was in remission at the time of death. This death was most likely related to underlying hypercoagulable state, family history of heart disease and personal history of tobacco use.

Overall, the most common cause of death was PD. The fatal AE rate is 2% in axicabtagene ciloleucel arm and 1% in SOC arm which is fairly balanced across both the study arms.

Serious Adverse Events

The Applicant's Position:

Among subjects in the axicabtagene ciloleucel or the SOCT arm, 85 subjects (50%) and 77 subjects (46%), respectively, had at least 1 SAE. The most frequently (in ≥ 5% of subjects) reported SAEs of any grade in each treatment arm in the axicabtagene ciloleucel arm were pyrexia (16%), encephalopathy (10%), hypotension, (9%), and aphasia and pneumonia (5% each). The most frequently (in ≥ 5% of subjects) reported SAEs of any grade in the SOCT arm were febrile neutropenia (13%) and acute kidney injury and pyrexia (5% each). Additional information is provided in m5.3.5.1, ZUMA-7, Primary Analysis CSR, Section 11.4.

The FDA's Assessment:

Serious Adverse Events:
An SAE was defined as an AE that met at least one of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires subject hospitalization (including overnight stay) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

Events that required an escalation of care when the subject is already hospitalized were recorded as an SAE. Examples of such events include movement from routine care in the hospital to the ICU or if that event resulted in a prolongation of the existing planned hospitalization. If an investigator considered an event to be clinically important but it did not meet any of the seriousness criteria, then the event could still be classified as a SAE with the criterion of "other medically important serious event".

Axicabtagene ciloleucel arm:
Among the 168 subjects in the safety analysis set (SAS), SAEs occurred in 84 subjects (50%), while Grade ≥3 SAEs occurred in 70 subjects (42%). SAEs that occurred in ≥1% of the subjects are presented below.

Table 32. FDA - SAEs Occurring in ≥ 1% of Axicabtagene Ciloleucel Safety Population (N=168)

Adverse Events	All Grades N (%)	Max Toxicity Grade 3-5 N (%)
Cytokine Release Syndrome	29 (17%)	10 (6%)
Pyrexia	27 (16%)	1 (0.6%)
Encephalopathy*	26 (16%)	20 (12%)
Hypotension*	16 (10%)	7 (4%)

Adverse Events	All Grades N (%)	Max Toxicity Grade 3-5 N (%)
Infections-pathogen unspecified	13 (8%)	10 (6%)
Pneumonia*	9 (5%)	7 (4%)
Aphasia	8 (5%)	7 (4%)
Viral infectious disorders	6 (4%)	5 (3%)
Neutropenia*	6 (4%)	5 (3%)
Arrhythmia*	5 (3%)	3 (2%)
Tremor	5 (3%)	1 (0.6%)
Fatigue*	4 (2%)	2 (1%)
Febrile neutropenia	4 (2%)	4 (2%)
Headache*	4 (2%)	3 (2%)
Sepsis*	4 (2%)	4 (2%)
Tachycardia*	4 (2%)	2 (1%)
Abdominal pain*	3 (2%)	2 (1%)
COVID 19	3 (2%)	3 (2%)
Delirium *	3 (2%)	3 (2%)
Dyspnea*	3 (2%)	3 (2%)
Hypoxia	3 (2%)	1 (0.6%)
Motor dysfunction*	3 (2%)	2 (1%)
Renal insufficiency*	3 (2%)	2 (1%)
Bacterial infectious disorder	2 (1%)	2 (1%)
Fall	2 (1%)	2 (1%)
Hyponatremia*	2 (1%)	2 (1%)
Musculoskeletal pain*	2 (1%)	0
Neuropathy peripheral*	2 (1%)	2 (1%)
Respiratory failure*	2 (1%)	2 (1%)
Tachypnea	2 (1%)	1 (0.6%)
Upper respiratory tract infection	2 (1%)	2 (1%)
Fungal infectious disorder	1 (0.6%)	1 (0.6%)

*Source: FDA analysis of ADAEFDA dataset *Grouped Term*

Reviewer comment:

1. Because febrile neutropenia was re-adjudicated based on overlapping AEs of fever and neutropenia, the SAE flag in the ADAEFDA datasets does not represent the true incidence of serious febrile neutropenia.
2. The label will include non-laboratory SAEs occurring in >5 % of the safety population. This included CRS, fever, encephalopathy, hypotension, infection with unspecified pathogen and pneumonia. The SAEs in the dataset includes the individual signs and symptoms of CRS and NT.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

An overall summary of TEAEs in ZUMA-7 is provided in Table 33.

Table 33. Applicant - Kite ZUMA-7 Overall Summary of TEAEs (SAS)

	Axicabtagene Ciloleucel (N = 170) n (%)	Standard of Care (N = 168) n (%)
Any TEAE	170 (100)	168 (100)
Worst Grade ≥ 3	155 (91)	140 (83)
Worst Grade 5	14 (8)	7 (4)
Worst Grade 5, excluding PD	7 (4)	2 (1)
Any serious TEAE	85 (50)	77 (46)
Worst Grade ≥ 3	72 (42)	67 (40)
Worst Grade 5	14 (8)	6 (4)[a]
Worst Grade 5, excluding PD	7 (4)	2 (1)
Any treatment-related TEAE	163 (96)	160 (95)
Worst Grade ≥ 3	112 (66)	131 (78)
Worst Grade 5	1 (1)	2 (1)
Worst Grade 5, excluding PD	1 (1)[b]	2 (1)
Any serious treatment-related TEAE	63 (37)	59 (35)
Worst Grade ≥ 3	49 (29)	51 (30)
Worst Grade 5	1 (1)	2 (1)
Worst Grade 5, excluding PD	1 (1)	2 (1)
Any TE neurologic event	102 (60)	33 (20)
Worst Grade ≥ 3	36 (21)	1 (1)
Any serious TE neurologic event	34 (20)	1 (1)
Worst Grade ≥ 3	26 (15)	0 (0)
Any TE CRS	157 (92)	NA
Worst Grade ≥ 3	11 (6)	NA
Any serious TE CRS	29 (17)	NA
Worst Grade ≥ 3	10 (6)	NA
Any TE hypogammaglobulinemia	19 (11)	1 (1)
Worst Grade ≥ 3	0 (0)	0 (0)
Any TE cytopenias	136 (80)	135 (80)
Worst Grade ≥ 3	128 (75)	126 (75)
Any TE infections	70 (41)	51 (30)

	Axicabtagene Ciloleucel (N = 170) n (%)	Standard of Care (N = 168) n (%)
Worst Grade ≥ 3	24 (14)	19 (11)
Worst Grade 5	5 (3)	0 (0)

Data cutoff date = 18MAR2021.

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; PD, progressive disease; SAS, Safety Analysis Set; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

Notes: TEAE includes all AEs with an onset on or after the axicabtagene ciloleucel infusion date in the axicabtagene ciloleucel arm or the first dose of salvage chemotherapy in the standard of care arm. Subjects were summarized at their worst CTCAE grade or Lee Grade for CRS. AEs are graded per CTCAE version 4.03 and CRS events are graded according to a modified grading system proposed by Lee and colleagues {Lee 2014}. For axicabtagene ciloleucel arm, treatment-related TEAEs include TEAEs that are related to axicabtagene ciloleucel; for standard of care therapy arm, treatment-related TEAEs include TEAEs that are related to salvage chemotherapy, total body irradiation (given as part of conditioning for autologous stem cell transplant), high-dose chemotherapy, and autologous stem cell transplant. Grade 5 AEs were included in the table only when the value was nonzero; the PT for PD was B-cell lymphoma.

a One subject with a Grade 5 TEAE of B-cell lymphoma was not reported as an SAE by the investigator.

b. Another subject in the axicabtagene ciloleucel arm had a Grade 5 TEAE of progressive multifocal leukoencephalopathy that was deemed by the investigator to be related to lymphodepleting chemotherapy. This event is not included here because "treatment-related" refers to events related to axicabtagene ciloleucel or standard of care therapy.

Source: m5.3.5.1, ZUMA-7 Primary Analysis Clinical Study Report, Table 33.

Events considered adverse drug reactions (ADRs) for axicabtagene ciloleucel in the r/r LBCL population are based on a review of all AEs in ZUMA-7. Symptoms of CRS were captured in the incidence of their respective ADRs as well as in the incidence of CRS. Frequencies of ADRs for anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, ALT increased, AST increased, bilirubin increased, blood uric acid increased, direct bilirubin increased, hypocalcemia, hypokalemia, hyponatremia, hyperglycemia, hypoalbuminemia, and hypophosphatemia were calculated using the laboratory values. All ADR frequencies are provided at the subject level (ie, the same ADR term was counted only once per subject). ADR frequency categories are defined according to the Council for International Organizations of Medical Sciences conventions as follows: very common (≥ 1/10)common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

The most common adverse reactions (incidence ≥ 20% of subjects) in the axicabtagene ciloleucel arm in order of decreasing frequency include fever, CRS, fatigue, encephalopathy, hypotension, tachycardia, diarrhea, headache, nausea, musculoskeletal pain, chills, cough, tremor, transaminases increased, unspecified pathogen infections, dizziness, decreased appetite, hypoxia, edema, abdominal pain, and constipation.

The most common (incidence ≥ 10% of subjects) Grade 3 or higher reactions in order of decreasing frequency included leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia, encephalopathy, hyponatremia, hyperglycemia, and hypotension.

The Applicant's Position:

Risks associated with axicabtagene ciloleucel have been well-characterized and no new safety

signals were identified relative to those observed in r/r LCBC.

The FDA's Assessment:

Overview of the Adverse Events:
Axicabtagene Ciloleucel Arm:
AEs and SAEs were evaluated during clinic visits, hospitalizations, and follow-up visits per protocol-defined guidelines. The clinical safety review was primarily based on analysis of 168 subjects that were randomized to the axicabtagene ciloleucel arm and treated with the conformal product. Two subjects that were treated with non-conforming axicabtagene ciloleucel were excluded from the safety analysis set.

All 168 subjects (100%) had at least one AE. AEs and SAEs are events that occurred after the administration of axicabtagene ciloleucel. Table 34 presents an overview of all AEs with data cut- off of March 18, 2021 which is similar to the data cut-off used for efficacy analysis. The majority of the maximum toxicity grades were Grade 3 or 4 events.

Table 34. FDA - Summary of Treatment-Emergent Adverse Events

Parameter	Axicabtagene ciloleucel safety population N=168 n (%)
All Grade AEs	168 (100%)
Max Grade 3-5 AEs	153 (91%)
Max Grade 3 AEs	33 (20%)
Max Grade 4 AEs	106 (63%)
Max Grade 3 or 4 AEs	139 (83%)
AEs leading to death*	3 (2%)
SAEs	84 (50%)

*Excludes deaths from PD. Includes encephalopathy, PML and sepsis.
Source: FDA analysis of ADAEFDA dataset

Reviewer comment:
Several information requests were sent the Applicant to verify and re-adjudicate several AEs. The reviewer requested the resubmission of updated datasets (ADAE, ADCRS, ADNE, ADSAF) that reflect FDA's review and re-adjudication and FDA GT. The following datasets were submitted on 26 January 2022 under 125634/394/14 eSeq 431 which were used for the analysis: ADAEFDA, ADCRSFDA, ADNEFDA, ADSAFFDA, and ADCRNFDA. Data structure for these datasets are identical to the original version ADAE, ADCRS, ADNE, ADSAF, and ADCRNFDA datasets respectively. Dataset ADSAFFDA was updated by the Applicant and resubmitted on 3 February 2021 under 125634/394/18 eSeq 437 to add parameter= NTSU01FL to identify the 124 subjects that were adjudicated as having NT. ADCRNFDA was updated to add flags to identify 124 subjects (NTSU01FL) and the 594 events (ie, NTEV01FL). Three NT events which

occurred after the subsequent therapy are not in the ADCRNFDA dataset and were submitted in a separate excel file. An updated ADAEFDA dataset was submitted on 7 February 2022 under 125643/394/21 which included flags AELK01FL and AECC01FL to identify the AEs that occurred in the leukapheresis and conditioning chemotherapy period.

Table 35. FDA - All Grade Non-Laboratory AEs in ≥ 10% of Subjects in Axicabtagene Ciloleucel Arm (N=168)

TEAE by Body System Organ Class	All Grades n (%)	Max Grades 3 - 5 n (%)
Any TEAE	168 (100%)	153 (91%)
Blood and lymphatic system disorders		
Febrile neutropenia	52 (31%)	52 (31%)
Cardiac disorders		
Tachycardia*	73 (43%)	4 (2%)
Arrhythmia*	24 (14%)	5 (3%)
Gastrointestinal disorders		
Diarrhea*	70 (42%)	5 (3%)
Nausea	67 (40%)	3 (2%)
Abdominal pain*	34 (20%)	6 (4%)
Constipation	34 (20%)	0
Vomiting*	33 (20%)	0
Dry Mouth	16 (10%)	0
General disorders and administration site conditions		
Pyrexia	156 (93%)	15 (9%)
Fatigue*	87 (52%)	11 (7%)
Chills	47 (28%)	1 (0.6%)
Edema*,#	39 (23%)	2 (1%)
Immune system disorders		
Cytokine Release Syndrome	155 (92%)	11 (7%)
Hypogammaglobulinemia	18 (11%)	0
Infections and infestations		
Infections: pathogen unspecified	42 (25%)	13 (8%)
Viral infectious disorder	25 (15%)	6 (4%)
Fungal infectious disorder	17 (10%)	1 (0.6%)
Bacterial infectious disorder	17 (10%)	8 (5%)
Metabolism and nutrition disorders		
Decreased appetite	41 (24%)	7 (4%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	67 (40%)	2 (1%)
Motor dysfunction#,*	25 (15%)	6 (4%)
Nervous system disorders		

TEAE by Body System Organ Class	All Grades n (%)	Max Grades 3 - 5 n (%)
Encephalopathy*,#	78 (46%)	31 (18%)
Headache*	69 (41%)	5 (3%)
Dizziness*	42 (25%)	6 (4%)
Tremor*	42 (25%)	2 (1%)
Aphasia	34 (20%)	11 (7%)
Peripheral neuropathy*	19 (11%)	4 (2%)
Psychiatric disorders		
Insomnia*	21 (13%)	0
Delirium*	20 (12%)	7 (4%)
Renal and urinary disorders		
Renal insufficiency*	19 (11%)	4 (2%)
Respiratory, thoracic and mediastinal disorders		
Cough*	46 (27%)	1 (0.6%)
Hypoxia	36 (21%)	15 (9%)
Skin and subcutaneous tissue disorders		
Rash*,#	29 (17%)	1 (0.6%)
Vascular disorders		
Hypotension*	79 (47%)	19 (11%)

Source: ADAEFDA Dataset
Abbreviation: GT: group term.
All adverse events are listed independently whether they were part of CRS or not.
*See FDA grouped terms in Section 18.4, Table 63 (Appendix)

Other clinically important adverse reactions that occurred in <10% of subjects treated with axicabtagene ciloleucel include the following:

- Blood and lymphatic system disorders: Coagulopathy*(9%)
- Cardiac disorders: Cardiac failure* (1%)
- Eye Disorders: Visual impairment* (7%),
- Infections and infestations: Pneumonia* (8%) , Sepsis* (4%)
- Nervous System Disorders: Ataxia* (6%), Seizure (3%), myoclonus (2%), facial paralysis*(2%), paresis* (2%)
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea* (8%), pleural effusion(6%), respiratory failure* (2%)
- Vascular disorders: Hypertension (9%), thrombosis* (7%)

Reviewer comment:
1. The overall AEs noted after axicabtagene ciloleucel treatment in ZUMA-7 are consistent with those seen with other anti-CD19 CAR T products and with other axicabtagene ciloleucel studies ZUMA-1 and ZUMA-5. The AEs are considered of acceptable severity given subjects' high-risk disease. No new safety signal was observed.

2. Although the AEs are presented by SOC, some GTs include more than one SOC and are indicated with a # sign in Table 35 above. For example: encephalopathy includes nervous system disorders and psychiatric disorders SOCs. We placed these group term AEs under the SOC with most representation in the data for that AE and/or clinically most appropriate (e.g., encephalopathy and dizziness under nervous system disorders SOC).

3. Infections were classified by the pathogen type based on the high-level group terms (AEHLGT) (bacterial, viral, fungal etc.) and also based on common sites such as pneumonia or serious clinical syndrome such as sepsis with some infections included in both grouping. This approach was felt to be most informative to the prescribers. Two AEs (aspiration pneumonia and lung infiltration) from respiratory disorder SOC were included under the grouped term "pneumonia". A foot note may be included in the ADR table of the label to indicate that pneumonia encompasses more than one SOC and the subjects have been counted more than once in the GTs of pneumonia and sepsis.

4. The Applicant reported the AE of febrile neutropenia only in four subjects However, reviewer identified additional subjects with fever that overlapped with grade ≥3 neutropenia in the absence of systemic infection. The Applicant agreed with the reviewer that the 52 subjects had febrile neutropenia. Therefore, the incidence of febrile neutropenia was updated to 31% (52 of 168).

5. The GT hemorrhage occurred in 11 (7%) subjects and included the following preferred terms/SOCs:

- 2: Epistaxis (Respiratory, thoracic and mediastinal disorders)
- 1: Gastric hemorrhage, 1:hemorrhoidal hemorrhage, 1:hematemesis, 1:hematochezia (Gastrointestinal disorders)
- 2: Hematuria, 1:urinary tract hemorrhage (Renal and urinary disorders)
- 3: Hematoma (Vascular disorders)
- 1:Intracranial hemorrhage (Nervous system disorders)

<u>Reviewer comments pertinent to the adverse drug reaction (ADR) table of the label:</u>
1. The table above will serve as the basis for the ADR table of the label. The laboratory abnormalities incidence will be presented in a separate table that is derived from the ADLB dataset and not from the ADAE dataset since the ADLB is more accurate in capturing all laboratory abnormalities rather than just the ones recorded as AEs.
2. Hypogammaglobulinemia will be presented under the Immune system disorders SOC rather than Investigations SOC similar to what was done for ZUMA-1 and ZUMA-5.

Adverse events and deaths were also assessed for the period after randomization to the planned time of infusion to assess risks for subjects who did not receive axicabtagene ciloleucel due to adverse events or deaths.

One hundred and seventy-eight subjects underwent leukapheresis, however, ten subjects (6%) did not receive treatment with conformal axicabtagene ciloleucel including two subjects who

received non-conformal product (1%). Two subjects were reported dead before infusing (1%), two subjects had disease progression (1%), one subject was not treated due to absence of disease progression on reassessment (0.6%), one subject was found to be ineligible for study treatment due to Grade 2 ALT elevation (0.6%) and 2 subjects (1%) had LD related toxicity of CVA and small intestinal perforation respectively precluding further therapy.

Leukapheresis period:

This period is defined from the day of leukapheresis until the day before the start of conditioning chemotherapy. The leukapheresis population included 178 out of the 180 randomized subjects. The most common AEs occurring during this period include fatigue, abdominal pain, anemia, lymphopenia, fever and musculoskeletal pain. Two subjects died after leukapheresis and prior to receiving conditioning chemotherapy of whom one subject died from Grade 5 sepsis with progressive disease on study day 17 (8 days after leukapheresis) and one subject died due to progressive disease on study day 17 (13 days after leukapheresis). Both deaths are deemed unrelated to the study procedure. Two subjects were unable to proceed to lymphodepleting chemotherapy:

- One subject developed AE of Grade 2 ALT increase from Study Day 16-22 rendering subject ineligible for conditioning chemotherapy and CAR T therapy. This subject subsequently received R-ICE due to inability to receive study treatment.
- One subject developed AE of Grade 3 hyperbilirubinemia from Study Day 17-21. He was subsequently noted to have clinical progression as cause of the lab abnormality. Clinical progression was confirmed by central assessment. This subject was subsequently treated with comfort measures.

One additional subject was unable to proceed to conditioning chemotherapy due to 1) disease progression and 2) another subject due to false progression at baseline which was not demonstrated on reassessment.

Table 36. FDA - Adverse Events During Leukapheresis

AEs	Analysis Population N=178
All Grade AEs	116 (65%)
Grade 3-5 AEs	36 (20%)
AEs leading to death	2 (1%)
All grade SAEs	22 (12%)
Grade 3-5 SAEs	18 (10%)

Source: FDA analysis of ADAEFDA dataset

Reviewer comment: The protocol specified that if any screening assessments were repeated between confirmation of eligibility and start of conditioning therapy and results of such assessment were outside the eligibility criteria, then subject would be considered ineligible unless the underlying abnormality resolved. This resulted in exclusion of two subjects who were eligible at screening but developed lab abnormality post leukapheresis precluding further therapy.

Conditioning chemotherapy period (CC):

The conditioning chemotherapy period begins on the day of the first chemotherapy administration until the day immediately prior to the axicabtagene ciloleucel infusion. The CC population included 172 subjects. The most common AEs that occurred during this period include nausea, lymphopenia, vomiting, anemia, constipation and fever. Two subjects treated with conditioning chemotherapy were unable to receive axicabtagene ciloleucel. Brief narratives are provided below:

- One subject developed disease related hypercalcemia requiring hospitalization. During hospitalization, subject developed malignant hydronephrosis, acute kidney injury followed by acute respiratory distress and pulmonary edema. Following diuresis and resolution of hypercalcemia, subject was treated with lymphodepleting chemotherapy from Study Day 25-27 . However, clinical course was complicated with hypoxic respiratory failure requiring intubation and new onset right sided hemiplegia due to Grade 3 ischemic left CVA on Study Day 27. The CVA rendered subject ineligible for further clinical trial participation. Subject eventually died from Grade 5 respiratory distress on Study Day 33. The AE of ischemic stroke is considered related to lymphodepleting chemotherapy.
- One subject was treated with bridging steroids followed by lymphodepleting chemotherapy from Study Days 41-43. This subject developed Grade 2 small intestinal perforation on Study Day 46. This was managed conservatively with IV antibiotics. Subject died from PD on Study Day 160. The AE of intestinal perforation is considered possibly related to the lymphodepleting chemotherapy and bridging corticosteroids.

Table 37. FDA - Adverse Events During Conditioning Chemotherapy

AEs	Analysis Population N=172
All Grade AEs	128 (74%)
Grade 3-5 AEs	55 (32%)
AEs leading to death	1 (0.6%)
All grade SAEs	14 (8%)
Grade 3-5 SAEs	4 (2%)

Source: FDA analysis of ADAEFDA dataset

Reviewer comment: Toxicity profile is consistent with commonly anticipated adverse events from lymphodepleting chemotherapy.

Bridging therapy period:
Out of the 168 subjects in the safety analysis set, 58 subjects (35%) received bridging corticosteroids. The median cumulative dose of bridging corticosteroid was 5008 mg of cortisone equivalent with a median duration of 5 days (Range from 2 -26 days). Since bridging corticosteroids was administered to subjects with high disease burden at screening, a comparative toxicity analysis between subjects that received bridging versus no bridging is likely confounded by underlying disease burden, is unlikely to be informative and therefore is not performed.

Adverse Events of Special Interest (AESI)

The Applicant's Position:

AEs of special interest include identified and potential risks, which are described in Section 8.2.5. TEAEs that have been identified as important risks associated with axicabtagene ciloleucel treatment include neurologic events, CRS, cytopenias, infections, and hypogammaglobulinemia. TEAEs that had been identified as important potential risks include secondary malignancies, immunogenicity (associated with the presence of antibodies to the axicabtagene ciloleucel CAR), RCR, tumor lysis syndrome, and aggravation of GVHD.

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

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Axicabtagene ciloleucel is administered as a single infusion. No subjects discontinued treatment due to TEAEs in the axicabtagene ciloleucel arm.

Two subjects in the SOCT arm discontinued treatment due to TEAEs of Grade 4 acute kidney injury and Grade 1 blood stem cell harvest failure.

The FDA's Assessment:
In total, three subjects in the SOC arm were unable to tolerate protocol specified chemotherapy due to toxicities resulting in treatment discontinuation: two subjects discontinued R-ICE and R-DHAP respectively due to renal impairment and one subject was unable to tolerate R-GDP. One subject was unable to complete HSCT due to stem cell harvest failure.

Table 38. FDA - Subject Disposition of Safety Analysis Population in ZUMA-7

Parameter	Axicabtagene Ciloleucel N=168 n (%)	Standard of Care Arm N=168 n (%)
End of study status		
Ongoing	103 (61%)	82 (49%)
Discontinued	65 (39%)	86 (51%)
Reason for study discontinuation		
Total	168	168
Death	63 (38%)	75 (45%)
Lost To Follow Up	2 (1%)	2 (1%)
Investigator Decision	0	1 (0.6%)
Other	0	1 (0.6%)
Subject withdrawal of consent from further follow-up	0	7 (4%)

Source: FDA analysis of ADSL dataset

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

The Applicant's Position:

Axicabtagene ciloleucel is administered as a single infusion, and as such no subjects had a dose interruption or reduction due to TEAEs in the axicabtagene ciloleucel arm.

In the SOCT arm, there were 30 subjects had at least one TEAE with action of dose interruption or reduction to salvage chemotherapy.

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

Laboratory Findings

Data:

The 3 most common increased laboratory values with worsening grade shifts from predose in the axicabtagene ciloleucel arm were glucose (116 subjects, 68%), ALT (106 subjects, 62%), and AST (91 subjects, 54%); and in the SOCT arm were creatinine (124 subjects, 74%), glucose (89 subjects, 53%), and ALT and alkaline phosphate (51 subjects each, 30%).

The 3 most common increased laboratory values with worsening grade shifts of worst Grade 3 or higher in the axicabtagene ciloleucel arm were glucose (19 subjects, 11%), ALT (11 subjects, 6%), and AST (10 subjects, 6%); and in the SOCT arm were glucose (7 subjects, 4%), ALT (6 subjects, 4%), and AST (3 subjects, 2%).

The 3 most common decreased laboratory values with worsening grade shifts from predose in the axicabtagene ciloleucel arm were leukocytes (166 subjects, 98%), neutrophils (162 subjects, 95%), and calcium (151 subjects, 89%); and in the SOCT arm were hemoglobin (145 subjects, 86%), platelets (128 subjects, 76%), and lymphocytes (127 subjects, 76%). The 3 most common decreased laboratory values with worsening grade shifts of worst Grade 3 or higher in the axicabtagene ciloleucel arm were leukocytes (159 subjects, 94%), neutrophils (156 subjects, 92%), and lymphocytes (144 subjects, 85%); and in the SOCT arm were platelets (105 subjects, 63%), lymphocytes (101 subjects, 60%), and leukocytes (94 subjects, 56%).

The Applicant's Position:

These laboratory abnormalities were expected and consistent with results observed in subjects with aggressive lymphomas. Additional information is provided in m5.3.5.1, ZUMA-7, Primary Analysis CSR, Section 11.6.

The FDA's Assessment:

Routine clinical safety assessments included clinical laboratory analyses, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Specialty tests were conducted for replication competent retrovirus (RCR) and antibodies to axicabtagene ciloleucel. Toxicity grading was based on CTCAE version 4.03 criteria. The most common Grade 3 and 4 laboratory abnormalities that occurred in ≥10% of subjects included: leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia, hyponatremia and hyperglycemia. See Table 39 for details. Note that post- axicabtagene ciloleucel infusion lab toxicity includes lab toxicities observed on or after the axicabtagene ciloleucel infusion date while baseline lab assessment is defined as the last value taken prior to the first dose of conditioning chemotherapy.

Table 39. FDA - Grade 3-4 Laboratory Abnormalities in the Axicabtagene Ciloleucel Arm

Laboratory test	Axicabtagene Ciloleucel Grade 3-4, n (%)
WBC decrease	160/168 (95)
Neutrophil count decrease	158/168 (94)
Lymphocyte count decrease	158/168 (94)
Hemoglobin decrease	68/168 (40)
Platelet decrease	44/168 (26)
Sodium decrease	20/168 (12)
Glucose increase	19/168 (11)
Calcium decrease	13/168 (8)
Potassium decrease	11/168 (7)
ALT increase	10/168 (6)
AST increase	9/167 (5)
Creatinine increase	6/168 (4)
Albumin decrease	5/167 (3)
Magnesium decrease	4/168 (2)
Bilirubin increase	3/168 (2)
Calcium increase	3/168 (2)
Magnesium increase	1/168 (1)
Alkaline phosphatase increase	1/168 (1)

Percentages are based on the number of evaluable subjects defined as subjects with both a baseline grade and at least one post-baseline grade for particular lab.
Source: Applicant IR dated 2/10/2022

Reviewer comment:
1.The pre-infusion baseline flag in the original ADLB dataset included the latest laboratory value prior to the infusion of axicabtagene ciloleucel. This flag included labs that were collected after start of lymphodepleting chemotherapy (LD) (Day -4 to -1) in 21 subjects. Considering labs drawn after receipt of conditioning chemotherapy (LD) as baseline could result in under-estimation of post- CAR T lab toxicity grades, especially for hematological parameters since LD can cause hematological toxicity on its own. Therefore, reviewer requested that Applicant re-submit ADLB dataset in which baseline labs are uniformly defined as labs drawn on Day -5 (prior to first dose of LD) or earlier. Additional columns were requested in the dataset that 1) identify

both grade and directionality of baseline toxicity and treatment emergent toxicity 2) describe change from baseline grade to post-treatment grade, for example for a change from grade 3 hypokalemia at baseline to grade 3 hyperkalemia would be -3 to +3 , 3) flag treatment emergent lab abnormalities that are new or worsened from baseline. Updated ADLBFDA datasets were submitted on February 22, 2022 under 125643/394/25 e seq 447.

2. The denominators for laboratory analyses in Table 39 are based on subjects with a baseline value and at least one post-treatment value. Subjects must have had at least one grade worsening on study to be counted in analysis and only worst toxicity grade are included in this analysis. While the approach of using a different denominator for each lab value based on the evaluable subjects (defined as subjects with both baseline grade and post-treatment grade available) is different than the approach used in ZUMA 1 and ZUMA-5 which used the safety population as the denominator, this approach is felt to more accurately capture the laboratory toxicity for the study population and is consistent with the current labeling practice.

Vital Signs

The Applicant's Position:

The investigator was responsible for reviewing all vital sign findings. Medical and scientific judgment was to be exercised when deciding whether an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality was a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) was to be recorded on the eCRF. Clinically significant changes in vital signs in the absence of a diagnosis or syndrome are not considered a risk of treatment with axicabtagene ciloleucel. Changes in vital signs are common in the setting of CRS; see Section 8.2.5 for an analysis of CRS.

The FDA's Assessment:
The STDM.VS domain included vital signs collected at scheduled visits and for only limited data points during the occurrence of AEs. During the safety review, the Applicant obtained some of the missing vital signs from the study sites to facilitate Agency's review of safety narratives.

Electrocardiograms (ECGs) (Delete if not applicable to the product)

The Applicant's Position:

ECGs were monitored as part of the safety assessments. Changes in ECGs may occur in the setting of CRS; see Section 8.2.5 for an analysis of CRS.

The FDA's Assessment:
FDA agrees that ECG were monitored as part of the safety assessment.

Immunogenicity

The Applicant's Position:

Immunogenicity to axicabtagene ciloleucel was evaluated by reactivity in a screening enzyme linked immunosorbent assay (ELISA) followed by a different confirmatory cell-based assay. Based on the initial screening ELISA, 8 subjects (5%) treated with axicabtagene ciloleucel were antibody-positive at baseline, and 9 subjects (5%) (including 1 subject with a negative result at baseline) were antibody-positive at any time point. All 9 subjects were antibody negative at all time points tested when assessed with a confirmatory cell-based flow cytometry assay.

Additional information is provided in Section 8.2.5, under potential risks.

The FDA's Assessment:
FDA agrees with the assessment that eight subjects were positive for anti-FMC 63 antibodies at baseline (pre-infusion) and one subject who was negative at baseline, tested positive post-infusion with ELISA which was a screening assay. All of these subjects were negative when tested with the confirmatory flow cytometry assay.

8.2.5. Analysis of Submission-Specific Safety Issues

Data:

TEAEs of special interest observed in ZUMA-7 are summarized below; additional information is in m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 11.2.6.

Important Identified Risks

Neurologic Events
In the SAS, 102 subjects (60%) in the axicabtagene ciloleucel arm and 33 subjects (20%) in the SOCT 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 subject in either treatment arm had a Grade 5 neurologic event.

The most frequently reported (≥ 10% of subjects) 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 SOCT arm; the most frequently reported neurologic events in the SOCT arm were paresthesia (14 subjects, 8%), delirium (5 subjects, 3%), and confusional state (4 subjects, 2%).

The most frequently reported (≥ 5% of subjects) worst Grade 3 or higher 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 SOCT arm had a Grade 3 or higher neurologic event of delirium.

Treatment-related neurologic events were reported for 92 subjects (54%) in the axicabtagene ciloleucel arm and 24 subjects (14%) in the SOCT arm, including Grade 3 or higher neurologic events in 35 subjects (21%) and 1 subject (1%), respectively. The most frequently reported (≥

10% of subjects) treatment related neurologic events of any grade in the axicabtagene ciloleucel arm were tremor (37 subjects, 22%), confusional state (35 subjects, 21%), aphasia (35 subjects, 21%), encephalopathy (29 subjects, 17%), and somnolence (18 subjects, 11%). No treatment-related neurologic events occurred with a subject incidence higher than 10% in the SOCT arm; the most frequently reported treatment related neurologic events were paresthesia (9 subjects, 5%), agitation, lethargy, cognitive disorder, depressed level of consciousness, delirium, and taste disorder (2 subjects each, 1%).

Serious treatment-emergent neurologic events of any grade were reported for 34 subjects (20%) in the axicabtagene ciloleucel arm and 1 subject (1%) in the SOCT arm, including 26 subjects (15%) in the axicabtagene ciloleucel arm with a serious Grade 3 or higher neurologic event and 1 subject (1%) in the SOCT arm with a serious worst Grade 2 neurologic event. Serious treatment-related neurologic events were reported for 32 subjects (19%) in the axicabtagene ciloleucel arm, including 25 subjects (15%) with Grade 3 or higher serious neurologic events; no subject in the SOCT arm had a serious treatment-related neurologic event. The most frequently reported (≥ 2% of subjects) serious treatment related neurologic events of any grade in the axicabtagene ciloleucel arm were encephalopathy (17 subjects, 10%), aphasia (9 subjects, 5%), and confusional state, somnolence, and tremor (5 subjects each, 3%).

Among subjects who had treatment-emergent neurologic events, the median time to onset was 7.0 days (range: 1 to 133 days) after the axicabtagene ciloleucel infusion and 23.0 days (range: 1 to 108 days) after the first dose of standard of care salvage chemotherapy. At the data cutoff date, neurologic events had resolved in 96 of the 102 subjects in the axicabtagene ciloleucel arm and in 32 of the 33 subjects in the SOCT arm; among these subjects, the median duration of neurologic events was 8.5 days (range: 1 to 817 days) and 23.0 days (range: 1 to 253 days), respectively. It should be noted that duration of neurologic events was calculated across all events regardless of whether the events were consecutive, overlapping, or neither, and that the late-onset event leading to the maximum event duration of 817 days was not related to study therapy. A total of 6 subjects in the axicabtagene ciloleucel arm and 1 subject in the SOCT arm had ongoing neurologic events at the data cutoff date (1 subject in the axicabtagene ciloleucel arm and 1 subject in the SOCT arm) or unresolved neurologic events at the time of death (5 subjects in the axicabtagene ciloleucel arm). Details are provided in m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 11.2.6.1.1.

Neurologic events were also identified via a second search strategy that was based on the MedDRA system organ classes of psychiatric disorders and nervous system disorders; additional information and results are provided in the m5.3.5.1, ZUMA-7 Primary Analysis CSR Neurologic Events Addendum. Due to the broader nature of the system organ class search strategy, this strategy yielded more reports of neurologic events of any grade and unresolved neurologic events compared with the Topp-based search strategy. Across both treatment arms, the additional neurologic events captured with the system organ class search strategy were primarily low-grade and nonserious events, including headache, dizziness, insomnia, anxiety, and dysgeusia. The incidence of worst Grade 3 or higher neurologic events was similar using either search strategy. Differences between the 2 search strategies were more pronounced in the SOCT arm; this can be attributed to the relatively low incidence of neurologic events

identified in this arm using the Topp-based search strategy, which is targeted toward known toxicities associated with anti-CD19 immunotherapy. Overall, the comparison of the Topp-based and system organ class search strategies in the ZUMA-7 randomized controlled study demonstrate that the Topp-based search strategy more appropriately captures clinically relevant neurologic events occurring after treatment with axicabtagene ciloleucel.

Neurologic events were generally manageable with medical intervention.

The FDA's Assessment:

Neurotoxicity in axicabtagene ciloleucel arm:

Among 168 subjects treated with axicabtagene ciloleucel, 124 (74%) experienced one or more neurologic toxicity events that are considered related to axicabtagene ciloleucel by FDA analysis. Forty-two subjects (25%) experienced Grade 3 or higher events (Table 43). The following neurologic toxicity events occurred in ≥10% of subjects: encephalopathy, headache, tremor, dizziness, aphasia, delirium and peripheral neuropathy. The median time to onset from axicabtagene ciloleucel infusion was 5 days (Range 1-133 days; Q1, Q3: 3,7). The median time to maximal toxicity grade was 1 day with range of 1-841 days. NT resolved in 106 out of 124 subjects (85%). Median time to resolution of NT, when excluding ongoing NT events at the time of death or data cut-off, was 15 days (Range: 1-546 days; Q1, Q3: 8,69). Median duration of NT was 24 days with range of 1-968 days in all subjects including those with ongoing neurologic events at the time of death or at data cut-off (source: FDA analysis).

Neurologic toxicities occurred within first 7 days of product infusion for 104/124 (84%) of the affected subjects.

Table 40 summarizes all neurologic toxicity events that are deemed related to axicabtagene ciloleucel including events associated with classic ICANS such as encephalopathy, aphasia and tremor and other treatment emergent adverse events such as peripheral neuropathy, motor dysfunction, dysgeusia, facial paralysis etc.

Table 40. FDA - Neurologic Toxicity Symptoms Attributed to Axicabtagene Ciloleucel (N=168)

Neurologic Events	Grade 1-5 n (%)	Grade 3 or higher n (%)
All subjects with neurotoxicity	124 (74%)	42 (25%)
Encephalopathy*	78 (46%)	31 (18.5%)
Headache*	69 (41%)	5 (3%)
Tremor	42 (25%)	2 (1.2%)
Dizziness*	36 (21%)	4(2.4%)

Neurologic Events	Grade 1-5 n (%)	Grade 3 or higher n (%)
Aphasia	34 (20%)	11 (6.5%)
Delirium*	20 (12%)	7 (4%)
Neuropathy peripheral*	17 (10%)	4(2.4%)
Insomnia*	15 (9%)	0
Affective disorder*	13 (8%)	0
Motor dysfunction*	13 (8%)	6 (3.6%)
Ataxia*	10 (6%)	2 (1.2%)
Visual impairment*	7 (4%)	0
Dysgeusia*	6 (3.6%)	0
Seizure	5 (3%)	1 (0.6%)
Facial paralysis*	4 (2%)	1 (0.6%)
Diplopia	3 (1.8%)	0
Myoclonus	3 (1.8%)	0
Paresis*	3 (1.8%)	0
Akathisia	2 (1.2%)	0
Cerebellar syndrome	1 (0.6%)	0
Eyelid ptosis	1 (0.6%)	0
Hemorrhage*(intracranial)	1 (0.6%)	0
Hemianopia	1 (0.6%)	0
Myelitis	1 (0.6%)	0
Nerve compression	1 (0.6%)	0
Nystagmus	1 (0.6%)	0
Sensory disturbance	1 (0.6%)	0
Upper motor neuron lesion	1 (0.6%)	0

*Source: FDA analysis of ADAEFDA Dataset. *Grouped term*

Reviewer comments:
The Applicant defined neurologic toxicity by Topp based method which includes events identified based on known NT associated with anti-CD19 immunotherapy primarily blinatumomab (Topp et al, 2015[8]). 100 out of 168 subjects had treatment emergent NT identified by this method with Grade 3 or higher toxicity in 35 subjects. Out of these 100 subjects, the Applicant considered 90 subjects (90/168=54%) subjects with CAR T related neurotoxicity and 34 (34/168= 20%) with Grade ≥3 neurologic toxicity.

FDA's NT assessment is defined by the Applicant as the systemic organ class (SOC) search strategy and includes all adverse events under the MedRA SOC of Psychiatric Disorders and Nervous System Disorders. 136 out of 168 subjects had treatment emergent NT using FDA method. After reviewing the safety datasets, narratives and information requests, the reviewer identified additional AEs under other SOCs that were indicative of NT and overlapped with other neurologic events in 27 subjects with treatment emergent NT. These include AEs such as ataxia under General Disorders, diplopia and visual blurring under Eye/Ear Disorders, muscle weakness under Musculoskeletal Disorders and myelitis under Infections and Infestations. In addition, reviewer excluded 12 subjects with certain low grade and isolated AEs under Nervous System and Psychiatry SOC such as insomnia, dizziness , anxiety, syncope etc. as not indicative of NT. In total, FDA identified 34 additional subjects with CAR T related NT compared to Applicant's analysis.

In summary, 124 subjects had NT related to axicabtagene ciloleucel by FDA analysis, out of which 42 subjects had Grade 3 or higher events. (Refer to Table 40 and 43).

The information in the USPI is based on FDA's definition and re-adjudication of neurologic toxicity. Grading of neurologic toxicity was per CTCAE criteria version 4.0.
Refer to Table 41 and Table 42 below for AEs that were re-adjudicated per FDA analysis.

Table 41 summarizes other neurologic toxicity events that were not flagged per the SOC search strategy but adjudicated as NT by the clinical reviewer.

Table 41. FDA - FDA Adjudication: Additional Events Included as Neurologic Toxicity (from N of 168)

ID	AEDECOD term	AE grade	ASTDY - AENDY	Reviewer comment
(b) (6)	Muscular weakness	3	22-42	Higher grade event that overlaps with other NT events.
	Muscular weakness	1	10-15	Overlaps with other NT events and is indicative of NT.
	Vision blurred	1	6 -6	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	1	10-76	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	3 2 1	7-9 10-10 11-80	Overlaps with other NT events and is indicative of NT.
	Visual impairment	1	10-11	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	3 2	11-20 21-23	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	3 2	10-18 19-218	Overlaps with other NT events and is indicative of NT.
	Vision blurred	1	7-8	Overlaps with other NT events and is indicative of NT.
	Vertigo	1	1	Is indicative of NT and is followed by other NT events
	Muscular weakness	1	37-71	Overlaps with other NT events and is indicative of NT.
	Diplopia	1	13-14	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	1	14-91	Overlaps with other NT events and is indicative of NT.
	Vertigo	1	0-2	Is indicative of NT and is followed by other NT events
	Vestibular disorder	2	12-14	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	1 3 2 1	7-8 9-11 12-17 28-41	Overlaps with other NT events and is indicative of NT.
	Diplopia	1	8-9	Overlaps with other NT events and is indicative of NT.

Table 41. FDA - FDA Adjudication: Additional Events Included as Neurologic Toxicity (from N of 168)

ID	AEDECOD term	AE grade	ASTDY - AENDY	Reviewer comment
(b) (6)	Diplopia	1	14-31	Overlaps with other NT events and is indicative of NT.
	Gait disturbance	1 1	2-2 6-9	Overlaps with other NT events and is indicative of NT.
	Muscle twitching	2	6-10	Overlaps with other NT events and is indicative of NT.
	Gait disturbance	1	10-49	Overlaps with other NT events and is indicative of NT.
	Eyelid ptosis	1	2-5	Overlaps with other NT events and is indicative of NT.
	Gait disturbance	1 2 1	3-13 14-15 16-56	Overlaps with other NT events and is indicative of NT.
	Gait disturbance	1 2	11-13 16-17	Overlaps with other NT events and is indicative of NT.
	Muscular weakness	3 2	8-14 15-42	Overlaps with other NT events and is indicative of NT.
	Myelitis	2	60-546	Overlaps with other NT events and is indicative of NT.
	Vision blurred Muscular weakness	1 2	16-ongoing 16-76	Overlaps with other NT events and is indicative of NT.
	Muscular weakness Facial asymmetry Vision blurred	1 1 1	12-18 14-15 16-17	Overlaps with other NT events and is indicative of NT.
	Vision blurred	1	24-25	Overlaps with other NT events and is indicative of NT.
	Vertigo[1]	1	10	Is considered a symptom of NT in addition to CRS.
	Vision blurred[1]	1 1	11-18 19	Is considered a symptom of NT in addition to CRS. Overlaps with other NT events and is indicative of NT.

Source: ADAEFDA dataset, safety narratives and IRs

[1] *AE was also considered a manifestation of CRS per investigator*

Given the nature of the following adverse events, the clinical context and in some cases isolated nature of their occurrence, these events were not considered NT events. These are summarized below in Table 42.

Table 42. FDA - FDA Adjudication: Events Excluded from Neurologic Toxicity (N=168)

USUBJID	AEDECOD	ADTSY-AENDY	Toxicity grade
(b) (6)	Dizziness	7-7	3
	Lumbar radiculopathy	63-75	2
	Insomnia	1-12	1
	Insomnia	19-ongoing	1
	Insomnia	18-26	1
	Dizziness	0-0	1
	Insomnia	1-32	1
	Syncope	96-96	3
	Dizziness	6-6	1
	Presyncope	33-33	2
	Sciatica	70-292	1
	Anxiety	8-16	1
	Dizziness	9-18	1
	Insomnia	20-89	2
	Insomnia	3-130	2

Source: ADAEFDA dataset, safety narratives and IRs

Table 43. FDA - Severity of Neurologic Toxicity in Axicabtagene Ciloleucel Arm (N=168)

Worst toxicity grade	n (%)
Any Grade	124 (74%)
1	41 (24%)
2	41 (24%)
3	32 (19%)
4	9 (5%)
5	1 (0.6%)

Source: FDA analysis of ADAEFDA Dataset

Overall, NT was unresolved in 18/124 affected subjects (14.5%) at the time of data cut off. These are summarized below:

One subject (b) (6) had grade 4 encephalopathy ongoing at the time of death from progressive disease on treatment day 46. Neurologic events were ongoing at the time of death in 10 additional subjects. These AEs were reviewed and found to be low grade events (Grades 1 and 2) and included preferred terms of anxiety, depression, tremor, facial nerve disorder, hypoesthesia, dysgeusia , intracranial hemorrhage, altered mood and insomnia. Ten AEs were ongoing in 6 subjects at the time of data cut-off. These were Grade 1 or 2 AEs including PTs of anxiety, headache,

peripheral neuropathy, insomnia, blurred vision, memory impairment and paresthesias.

One subject (USUBJID (b) (6)) died from Grade 5 NT on treatment day 846. Please see narrative for this subject under Section 8.2.4, Deaths.

One subject (USUBJID: (b) (6) developed grade 2 myelitis on treatment day 60. MRI performed on day 99 demonstrated non-enhancing mild T2 hyperintensity and expansion of the lower thoracic cord suggestive of myelitis without cord compression. This was managed with pregabalin and resolved on day 546.

Management of neurologic toxicity:
Out of 124 subjects with NT, tocilizumab (with or without steroids) was administered for the management of NT in 25 subjects. Steroids (with or without tocilizumab) were administered to 58 subjects for the management of NT. 18 subjects received both tocilizumab and steroids for the management of NT. Seven subjects received only tocilizumab for the management of NT and 40 subjects only received systemic steroids for the management of NT. One subject (USUBJID: (b) (6) received siltuximab for management of CRS/NT with suboptimal response to steroids and one subject (USUBJID: (b) (6) received anakinra for the management of NT.

Table 44. FDA - Use of Steroids and Tocilizumab Categorized by the Grade of NT at Administration

Management	**Neurologic toxicity N=124**					
Medication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Tocilizumab, n(%)	13 (10)	9 (7)	6 (5)	2 (2)	0	25 (20)
Corticosteroids, n(%)	33 (27)	39 (31)	29 (23)	7 (6)	0	58 (47)

Source: Applicant IR dated February 24, 2022

Overlap of neurologic toxicity and CRS:
Out of the 124 subjects with neurotoxicity, neurologic toxicity occurred before CRS in 1 (0.8%) subject, during CRS in 110 (89%) subjects, and after CRS in 11 (9%) subjects. Two (2%) subjects had NT without CRS.

Reviewer comment:

1. The clinical reviewer took a broad view of the neurologic toxicity regardless of the category of NT and included both CNS processes such as encephalopathy, aphasia , tremor and peripheral nervous system events such as peripheral neuropathy, facial nerve palsy etc. Since LD is part of the CAR T treatment plan, an AE such as dysgeusia that could be secondary to

lymphodepleting chemotherapy was considered a NT event if it was treatment-emergent.

2. The ADCM dataset limited flags for tocilizumab and corticosteroid use for the management of NT identified per Topp-based strategy. Table 44 includes concomitant medications that were used for the management of FDA adjudicated NT events. This includes events such as headache, dizziness and vertigo that were considered as manifestation of both CRS and NT which may be included under steroids/tocilizumab use for both AESIs.

3. While the label provides advice regarding the use of tocilizumab and steroids for CRS and NT management, limited data exist to support any labelling recommendation for the use of alternative inhibitors of IL-6 or other cytokines such as siltuximab and anakinra.

4. Steroids were recommended for ≥Grade 2 neurologic toxicities in ZUMA-7 unlike ZUMA-1 (Cohorts 1 and 2) in which steroids were recommended for ≥Grade 3 NT. As noted in Table 44 above, 27% of subjects with NT received steroids for Grade 1 NT and 31% received steroids for Grade 2 NT. This indicates a shift in earlier management of NT by the treating investigators which is consistent with the current NT management guidance included in axicabtagene ciloleucel USPI (Table 2, Section 2.3).

5. Since the AE of myelitis was low- grade and resolved spontaneously without any intervention, we did not include this AE in Section 5.2. Myelitis is already included as AE under Section 6.3, Post marketing Experience.

The overall rate of NT (74% and 87%) and ≥Grade 3 NT events (25% and 31%) were numerically lower in ZUMA-7 compared to ZUMA 1. The lower rate of ≥Grade 3 NT events could be due to earlier use of steroids in NT management or may be related to the study population (second line vs. third or later line).

CRS (Axicabtagene Ciloleucel Arm Only)

Among the 170 subjects treated in the axicabtagene ciloleucel arm, 157 subjects (92%) had CRS; 8 subjects (5%) had worst Grade 3 CRS, 3 subjects (2%) had worst Grade 4 CRS, and no subject had Grade 5 CRS. The most frequently reported (≥ 5% of subjects with CRS) worst Grade 3 or higher CRS symptoms were hypotension (18 subjects, 11%), pyrexia (14 subjects, 9%), and hypoxia (13 subjects, 8%). The most frequently reported (≥ 2% of subjects) serious CRS symptoms of any grade were pyrexia (20 subjects, 12%), hypotension (15 subjects, 9%), and hypoxia (3 subjects, 2%).

Among subjects who had CRS, the median time to onset was 3.0 days (range: 1 to 10 days) after the axicabtagene ciloleucel infusion. At the data cutoff date, CRS had resolved in all subjects, with a median duration of 7.0 days (range: 2 to 43 days).

All reported events of CRS were generally considered to be related to axicabtagene ciloleucel treatment. CRS was manageable with medical intervention and generally resolved.

The FDA's Assessment:

CRS in axicabtagene ciloleucel arm:

CRS occurred in 155/168 (92%) of the axicabtagene ciloleucel treated subjects. 11 subjects (7%) experienced grade 3 or higher CRS event (Table 45). There were no deaths from CRS and CRS was not ongoing at the time of death in any subject. One hundred and twenty two out of the 155 subjects (78%) with CRS also experienced neurologic toxicity.

The median time from axicabtagene ciloleucel infusion to CRS onset was 3 days (Range 1-10 days). The median time from CRS onset to maximal CRS grade was 1 day (Range 1-10 days). The median duration for CRS was 7 days (Range 2-43 days). CRS resolved in all subjects.

Of the safety population (N=168), manifestations of CRS in ≥ 20% of subjects included fever, hypotension, tachycardia and chills. Grade ≥3 events that may be associated with CRS and that occurred in >1% of subjects include hypotension, fever, hypoxia, arrhythmia, fatigue, tachycardia, decreased appetite, dyspnea, headache, nausea, respiratory failure and transaminase increase.

Please refer to Table 46 below for details regarding the individual AEs that were considered manifestation of CRS.

Table 45. FDA - CRS Toxicity Grade

Worst CRS Toxicity Grade	Subjects, N=168
CRS Any Grade	155 (92%)
Grade 1	69 (41%)
Grade 2	75 (45%)
Grade 3	8 (5%)
Grade 4	3 (2%)
Grade 5	0

Source: FDA analysis of ADCRSFDA dataset

Table 46. FDA - CRS Symptoms in >1% of Safety Population

CRS Symptoms/AEs	All grade AE, n (%) N=168	Grade ≥3 AE, n(%) N=168
Total	155 (92%)	51 (30%)
Fever (GT)	154 (92%)	14 (8%)
Hypotension (GT)	70 (42%)	18 (11%)
Tachycardia (GT)	64 (38%)	4 (2%)
Chills	38 (23%)	0
Headache (GT)	32 (19%)	2 (1%)
Fatigue (GT)	31 (18%)	4 (2%)
Hypoxia	30 (18%)	12 (7%)
Nausea	17 (10%)	2 (1%)
Transaminases increased (GT)	16 (10%)	2 (1%)
Diarrhea (GT)	14 (8%)	1(0.6%)
Musculoskeletal pain (GT)	13 (8%)	0
Vomiting	11 (7%)	0
Arrhythmia (GT)	10 (6%)	4 (2%)
Decreased appetite (GT)	9 (5%)	3 (2%)
Renal insufficiency (GT)	6 (4%)	0
Tachypnea (GT)	5 (3%)	1(0.6%)
C-reactive protein increased	4 (2%)	1(0.6%)
Blood alkaline phosphatase increased	3 (2%)	0
Dyspnea (GT)	3 (2%)	2 (1%)
Edema (GT)	3 (2%)	1(0.6%)
Rash (GT)	3 (2%)	0

CRS Symptoms/AEs	All grade AE, n (%) N=168	Grade ≥3 AE, n(%) N=168
Hyperbilirubinemia (GT)	2 (1%)	0
Hypertension	2 (1%)	1(0.6%)
Hypophosphatemia (GT)	2 (1%)	0
Influenza like illness	2 (1%)	0
Respiratory failure (GT)	2 (1%)	2 (1%)

Source: FDA analysis of ADCRSFDA dataset

CRS symptoms that occurred in <1% of the safety population out of n of 168 include apnea, cardiac failure, cardiomyopathy, coagulopathy, cough, dizziness, hypothermia, pleural effusion, shock, tremor, urinary incontinence and visual impairment. For complete list of all CRS symptoms that occurred in ZUMA-7, please refer to Section 18.4, Appendix.

Reviewer comment:
Our review strategy of finding additional subjects with CRS included identifying fever or hypotension or hypoxia between Day 0 and Day 30 in the subjects who were not flagged as having CRS. We additionally searched for subjects not flagged as having CRS but who received tocilizumab or vasopressors. Corticosteroid use was not used to identify additional CRS cases as it was considered a low yield strategy since corticosteroids are generally used as adjunctive to tocilizumab for CRS management and may also be used for additional indications such as NT, treatment of progressive lymphoma, other AEs, hypersensitivity reactions etc.

We did not identify any new subjects as having CRS. Overall, we upgraded CRS grade in one subject (Grade 1 changed to Grade 2) and extended duration of CRS in 4 subjects. In addition, we identified four AEs that were not considered manifestations of CRS although they occurred during CRS and were considered as indication for tocilizumab that was administered for CRS. We included these AEs as manifestations of CRS. (Refer to Table 47 below.)

Brief narratives of FDA adjudicated CRS grade and duration:

1. USUBJID (b) (6) : Applicant assigned CRS Grade 2 from Days 1-7. Subject was administered oxygen 2L/mt on days 4-5 for hypoxia which overlapped with CRS. In addition, subject was also administered oxygen at 2L/mt on Days 6-10 for hypoxia due to sleep apnea. Given the absence of any clinical evidence of sleep apnea and due to the proximity of hypoxia to the CRS event, this event of hypoxia requiring oxygen was considered a manifestation of ongoing CRS . Therefore, the duration of CRS was extended to Days 1-10.

2. USUBJID (b) (6) Applicant assigned CRS Grade 2 from Days 2-7. Subject was administered oxygen at 2L/mt from days 5-7 which overlapped with CRS. In addition, subject had hypoxia and required oxygen at 2L/mt from Days 8-11 for obstructive sleep apnea. However, there was no supportive evidence for sleep apnea such as previous history, diagnostic work and use of CPAP etc. Given the proximity of the hypoxia to the CRS event, this was considered indicative of ongoing CRS. CRS duration was extended to Days 2-11.

3. USUBJID (b) (6): Applicant assigned CRS Grade 1 from Days 2-6. However, subject had hypoxia on days 5-6 and days 7-10 and was administered oxygen on days 5 to 7 at 2l/mt which overlapped with CRS. The Applicant stated that oxygen was administered for comfort with no evidence of clinically significant hypoxia, therefore the assigned CRS grade was 1. Per CRS grading (Lee criteria 2014), oxygen requirement <40% is considered Grade 2, regardless of the degree of hypoxia. Therefore, reviewer adjudicated CRS grade 2 for this AE.
This subject was subsequently intubated on day 7 for grade 4 NT (40% Fi02). Post-extubation on day 10-11, subject received O2 at 1L/mt. While the reviewer agrees that intubation was for grade 4 encephalopathy, ongoing CRS was likely contributory to respiratory failure. The serum IL-6 level was also analyzed in the context of clinical picture of CRS . It was peaking on Day 7 making it unlikely that CRS ended on Day 6. (Baseline serum IL-6 level was 3.2pg/ml and treatment Day 7 was 47.8pg/ml). Based on the overall clinical and laboratory data, CRS duration is increased to Days 2-11.

4. USUBJID (b) (6): Applicant assigned CRS Grade 4 from Days 1-6. Subject developed acute respiratory failure from Days 3-13 and was intubated for grade 4 NT on Day 5. Review of the cytokine data indicated that serum IL-6 was peaking at Day 6 (baseline 1.7 pg/ml and 39 pg/ml on Day 7) making it unlikely that CRS ended on Day 6. Based on the clinical and laboratory data , CRS was ongoing and contributed to acute respiratory failure. Therefore, the duration of CRS is extended to Days 1-13.

Table 47. FDA - AEs Adjudicated as CRS Symptoms (N=168)

USUBJID /CRS Grade and days	Treatment days tocilizumab was administered	Indication for tocilizumab	Reason why AE was included as manifestation of CRS.
(b) (6) Grade 2, Day 2-10	Day 4,5	Arial fibrillation G 2, Day 6-7	Atrial fibrillation can occur as manifestation of CRS and overlapped with CRS.
(b) (6) Grade 1, Day 1-16	Day 3,5	Hypotension G 2 Day 2-7	Hypotension can be manifestation of CRS and overlapped with CRS.
(b) (6) Grade 4, Day 1-6	Day 3,4	Acute respiratory failure G 4 Day 3-8, G 3 Day 9-13	See narrative #4 above
(b) (6) Grade 3, Day 1-8	Day 4,5	Fever G 2, Day 3-6.	Subject does have neutropenia overlapping with fever; however, fever could also be manifestation of CRS.

Source: ADAEFDA dataset

CRS management:

Out of the 155 subjects with CRS, 111 subjects received tocilizumab (with or without steroids) for the management of CRS and 41 subjects were treated with systemic steroids (with or without tocilizumab) for the management of CRS. 38 subjects received both tocilizumab and steroids for the management of CRS. 73 subjects were only treated with tocilizumab for management of CRS. CRS in three subjects were managed only with systemic steroids. For additional details, refer to Table 11, Concomitant Medications. One subject received siltuximab for the management of CRS/NT with suboptimal response to steroids (USUBJID: (b) (6)).

Table 48. FDA - Use of Steroids and Tocilizumab Categorized by the Grade of CRS at Administration

Management	CRS N=155				
Medication	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
Tocilizumab, n(%)	59 (38)	59 (38)	5 (3)	1 (1)	111 (72)
Corticosteroids, n(%)	19 (12)	22 (14)	5 (3)	3 (2)	41 (26)

Source: Applicant IR dated February 24, 2022

Table 49. FDA - Number of Tocilizumab Doses Administered for Management of CRS

Number of doses of Tocilizumab , n(%)	Axicabtagene ciloleucel arm N=155 with CRS n (%)
1	40 (26%)
2	27 (17%)
3	20 (13%)
4	15 (10%)
≥5	9 (6%)

Source: Applicant Information Request Dated January 6, 2022.

Reviewer comment:
The management of CRS was revised several times during the conduct of the protocol as additional knowledge about CRS management was incorporated in the IB. The management of CRS shifted towards earlier introduction of tocilizumab: from administration of tocilizumab for Grade 1 CRS that did not respond to 3 days of supportive care and ≥Grade 2 CRS (IB Version 4.1) to earlier use after 24 hours of supportive care for Grade 1 CRS and ≥Grade 2 CRS (IB Version 6.0). Table 48 shows that 38% of patients with CRS received tocilizumab for Grade 1 CRS and 12% of patients with CRS received corticosteroids for grade 1 CRS. CRS management employed in ZUMA-7 was different from ZUMA-1 (Cohorts 1 and 2) in which tocilizumab was recommended for Grade 2 CRS only in subjects with extensive co-morbidities or older age and for ≥Grade 3 CRS.

The paradigm for earlier intervention with tocilizumab and steroids in ZUMA -7 is consistent with the current CRS management guidance included in axicabtagene ciloleucel USPI (Table 1, Section 2.3)

While the overall incidence of CRS observed in ZUMA-7 is similar to that observed in ZUMA 1 (92% and 94%), the incidence of ≥Grade 3 CRS is lower in ZUMA 7 compared to ZUMA 1 (7% and 13%). This difference in the rate of ≥Grade 3 CRS may be due to earlier intervention in ZUMA-7, or it may be related to differences in the study population (second line versus third or later line population).

Cytopenias

Thrombocytopenia was reported for 50 subjects (29%) in the axicabtagene ciloleucel arm and 101 subjects (60%) in the SOCT arm, including 25 subjects (15%) and 95 subjects (57%), respectively, with worst Grade 3 or higher thrombocytopenia.

Neutropenia was reported for 122 subjects (72%) in the axicabtagene ciloleucel arm and 92 subjects (55%) in the SOCT arm, including 119 subjects (70%) and 91 subjects (54%), respectively, with worst Grade 3 or higher neutropenia. Note that for subjects who had neutropenia and pyrexia concurrently, investigators were instructed to record fever separately from neutropenia if the fever was attributed to CRS.

Anemia was reported for 73 subjects (43%) in the axicabtagene ciloleucel arm and 92 subjects (55%) in the SOCT arm, including 51 subjects (30%) and 65 subjects (39%), respectively, with worst Grade 3 or higher anemia.

Cytopenias that were present on or after Therapy day 30 after the first dose of axicabtagene ciloleucel or standard of care salvage chemotherapy (ie, prolonged cytopenias) were reported for 70 subjects (41%) and 117 subjects (70%) in the axicabtagene ciloleucel and SOCT arms, respectively, with lower incidences after axicabtagene ciloleucel treatment than SOCT for prolonged thrombocytopenia (32 subjects [19%] versus 85 subjects [51%], respectively) and prolonged anemia (23 subjects [14%] versus 84 subjects [50%], respectively), and a similar incidence for prolonged neutropenia (56 subjects [33%] and 61 subjects [36%], respectively). Worst Grade 3 or higher prolonged cytopenias that were present on or after Therapy day 30 were reported for 49 subjects (29%) and 101 subjects (60%), respectively, with lower incidences after axicabtagene ciloleucel treatment than SOCT for prolonged thrombocytopenia (11 subjects [6%] versus 78 subjects [46%]), neutropenia (44 subjects [26%] versus 60 subjects [36%]), and anemia (5 subjects [3%] versus 57 subjects [34%]), respectively.

The FDA's assessment:

Axicabtagene ciloleucel arm: Prolonged cytopenia

The incidence of prolonged cytopenias (that were present on or after Day 30 following the axicabtagene ciloleucel infusion on Day 0) based on analysis of the lab dataset (ADLB) is summarized in this section. Overall, any ≥ Grade 3 prolonged cytopenia was observed in 56 subjects (33%). The number of subjects who had worst Grade 3 or higher prolonged neutropenia, thrombocytopenia, and anemia were 53 (32%), 14 (8%), and 9 (5%) subjects respectively.

Reviewer comment:

The Applicant's original analysis for prolonged cytopenia was based on the ADAE dataset. Since the ADAE dataset only includes abnormal laboratory findings that are considered AEs in the investigator's judgement, ADAE dataset based analysis may underestimate the incidence of protocol defined prolonged cytopenia. Therefore, ADLB dataset based incidence of prolonged cytopenia is included in the USPI.

Infections

Infections, identified as AEs within the system organ class of infections and infestations, were reported for 70 subjects (41%) in the axicabtagene ciloleucel arm and 51 subjects (30%) in the SOCT arm, and 24 subjects (14%) and 19 subjects (11%), respectively, had worst Grade 3 or higher infections. Grade 5 infections were reported for 5 subjects (3%) in the axicabtagene

ciloleucel arm, including COVID-19 (2 subjects), PML (1 subject), hepatitis B reactivation (1 subject), and sepsis (1 subject); no subject in the SOCT arm had a Grade 5 infection.

The most frequently reported (≥ 2% of subjects) worst Grade 3 or higher TEAEs within the category of infection (excluding COVID-19) in the axicabtagene ciloleucel arm were pneumonia (6 subjects, 4%) and upper respiratory tract infection (3 subjects, 2%); and in the SOCT arm were pneumonia and sepsis (4 subjects each, 2%). COVID-19 infections were reported as TEAEs for 3 subjects (2%) in the axicabtagene ciloleucel arm (all were worst Grade 3 or higher) and 1 subject (1%) in the SOCT arm (Grade 1).

Serious infections were reported for 20 subjects (12%) in the axicabtagene ciloleucel arm and 16 subjects (10%) in the SOCT arm, including 17 subjects (10%) and 15 subjects (9%), respectively, with a worst Grade 3 or higher serious infection. The most frequently reported (≥ 2% of subjects) serious infections by PT in the axicabtagene ciloleucel arm were pneumonia (8 subjects, 5%) and COVID-19 (3 subjects, 2%), and in the SOCT arm were pneumonia and sepsis (4 subjects each, 2%).

The FDA's assessment:

Axicabtagene ciloleucel Arm:

Overall, 73 subjects (43%) had infections and 23 (14%) subjects had worst Grade ≥ 3 infections. Sixteen subjects (10%) had worst Grade 3 infections and three subjects (2%) had a worst Grade 4 event. Four subjects (2%) had Grade 5 infections including one case of progressive multifocal leukoencephalopathy, two cases of COVID 19 and one case of sepsis. The most common events by preferred terms within the SOC of Infections and Infestations included: oral candidiasis (14 subjects, 8%), upper respiratory infection (11 subjects, 6.5%), pneumonia (10, 6%) and urinary tract infection (7, 4%).

Details regarding infections by HLGT (high level grouped terms) and including pneumonia as an important site of infection and sepsis as clinically important syndrome are presented in Table 50. Table 51 summarizes the serious treatment emergent infections in the safety population.

Table 50. FDA - Treatment-Emergent Infections in the Safety Population

TEAE Infections	Axicabtagene Ciloleucel N = 168	
	Grade 1-5 n (%)	Grade 3-5 n (%)
Infections - pathogen unspecified	42 (25)	13 (8)
Febrile neutropenia*	52 (31)	52(31)
Pneumonia (GT)	13 (8)	8 (5)
Sepsis (GT)	7 (4)	6 (3.5)
Viral infections	25 (15)	6 (3.5)
Fungal infections	17 (10)	1 (0.6)
Bacterial infections	17 (10)	8 (5)

Source: FDA analysis of ADAEFDA dataset
Pneumonia GT includes two events (lung infiltration and aspiration pneumonia) from Lower respiratory tract disorders under Respiratory disorders SOC
Febrile neutropenia: fever and ≥Grade 3 neutropenia in the absence of documented systemic infection may overlap with CRS.

Table 51. FDA - Serious Treatment-Emergent Infections Occurring in > 1% of Safety Population

Serious TEAE Infections	Axicabtagene Ciloleucel N = 168	
	Grade 1-5 n (%)	Grade 3-5 n (%)
Infections - pathogen unspecified	13 (8%)	10 (6%)
Pneumonia (GT)	9 (5%)	7 (4%)
Sepsis (GT)	4 (2%)	4 (2%)
Viral infections	6 (4%)	5 (3%)
Fungal infections	1 (0.6%)	1 (0.6%)
Bacterial infections	2 (1%)	2 (1%)

Source: ADAEFDA dataset
Abbreviation: HLGTL high level group term

Reviewer comment:
1. Reviewer included one case of Grade 3 aspiration pneumonia and one case of Grade 1 lung infiltration under grouped term of pneumonia. These two events are classified under SOC of Respiratory Disorders and grouped under lower respiratory tract disorders.
2. One case of Grade 2 myelitis was excluded from infections as it was a NT event.
3. The Applicant reported AE of febrile neutropenia only in four subjects ((b) (6) However, 48 additional subjects had fever that overlapped with Grade ≥3 neutropenia in the absence of systemic infection. These were included under febrile neutropenia. Therefore, the incidence of febrile neutropenia was updated to 31% (52 of 168). Per CTCAE version 4 toxicity grading, all febrile neutropenia cases are considered Grade 3 or higher.
4. During the labeling negotiations, the Applicant proposed to categorize an AEDECOD term of bacteremia (reported as verbatim term Moraxella bacteremia) under bacterial infectious disorder as opposed to infections: pathogen unspecified category. The reviewer found this recategorization acceptable.
5. One subject with history of treated HBV (positive Hepatitis B core antibody and Hepatitis B surface antigen but negative HBV PCR) on chronic suppression with entecavir at enrollment was treated with non-conformal product . This subject developed Grade 5 fulminant hepatic failure on treatment day 422 due to reactivation of HBV after discontinuation of entecavir. Since this subject was treated with non-conformal product, this AE is excluded from Tables 50 and 51 above.

Hypogammaglobulinemia

Hypogammaglobulinemia TEAEs were reported for 19 subjects (11%) in the axicabtagene ciloleucel arm and 1 subject (1%) in the SOCT arm. All hypogammaglobulinemia events were

PTs of hypogammaglobulinemia, and all were worst Grade 1 (6 subjects, 4%) or Grade 2 (13 subjects, 8%) in the axicabtagene ciloleucel arm, and worst Grade 1 (1 subject, 1%) in the SOCT arm.

The FDA's Assessment:

Axicabtagene ciloleucel arm: Overall, 18/168 subjects (11%) in the safety analysis set had hypogammaglobulinemia (PT of hypogammaglobulinemia) reported as an adverse event. All hypogammaglobulinemia events were Grade 1 or 2. Hypogammaglobulinemia is likely to be underreported as it is based on the AE dataset rather than dedicated laboratory dataset.

Important Potential Risks

Important potential risks associated with axicabtagene ciloleucel include secondary malignancies, immunogenicity (associated with the presence of antibodies to the axicabtagene ciloleucel CAR), RCR, tumor lysis syndrome, and aggravation of GVHD. These TEAEs, with the exception of immunogenicity and RCR, were also collected for subjects in the SOCT arm.

No new malignancies were considered by Kite to be secondary to axicabtagene ciloleucel.

Based on the initial screening ELISA, 8 subjects (5%) treated with axicabtagene ciloleucel were antibody-positive at baseline, and 9 subjects (5%) (including 1 subject with a negative result at baseline) were antibody-positive at any time point. All 9 subjects were antibody-negative at all time points tested when assessed with a confirmatory cell-based flow cytometry assay.

Of the 150 subjects in the axicabtagene ciloleucel arm who had RCR data at any time point, none tested positive for RCR.

Tumor lysis syndrome was not reported for any subjects in the axicabtagene ciloleucel arm and was reported for 1 subject (1%) in the SOCT arm (Grade 3, nonserious, unrelated to SOCT).

No subjects experienced treatment-emergent aggravation of GVHD.

The Applicant's Position:

Risks associated with axicabtagene ciloleucel have been well-characterized and no new safety signals were identified relative to those observed in LBCL after 2 or more lines of therapy (ZUMA-1). CRS and neurologic events observed in ZUMA-7 were generally resolved and manageable with medical intervention and supportive care, and the rates of certain important identified risks (neurologic events, serious neurologic events, cytopenias, and Grade 3 or higher infections) were lower than those observed in patients with r/r LBCL after 2 or more lines of therapy (ZUMA-1).

The FDA's Assessment:
No new safety signals were identified in ZUMA-7 relative to those observed in subjects with r/r

LBCL after two or more lines of therapy (ZUMA-1) or follicular lymphoma after two or more lines of therapy (ZUMA-5). As noted earlier, CRS and NT were intervened at lower grades in ZUMA-7 compared to ZUMA-1 which may result in lower rate of ≥Grade 3 toxicities. Please refer to Section 8.2.11 for combined safety analysis of ZUMA-1, ZUMA-5 and ZUMA-7.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees that no information was included in this submission regarding COA to inform safety of axicabtagene ciloleucel.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses of TEAEs were performed for the subgroups defined by baseline characteristics, including response to first-line therapy, r/r subgroup, sAAIPI, disease type, geographic region, ECOG performance score, age, sex, race, and ethnicity. Generally, trends observed between treatment arms overall were maintained in subgroup analyses; differences of ≥ 10% between treatment arms are discussed.

In the axicabtagene ciloleucel and SOCT arms, 121 and 113 subjects, respectively, were < 65 years of age and 49 and 55 subjects, respectively, were ≥ 65 years of age. For subjects in both age groups, the percentage of subjects who experienced TEAEs, treatment-related TEAEs, and treatment-related SAEs were generally similar (< 10% difference) between treatment arms, whereas in the axicabtagene ciloleucel arm, more subjects ≥ 65 years of age had worst Grade 3 or higher TEAEs and SAEs compared with subjects ≥ 65 years of age in the SOCT arm (94% versus 82%, respectively, and 59% versus 47%, respectively). Subject incidence of TEAEs of interest with a difference ≥ 10% for subjects < 65 years of age in the axicabtagene ciloleucel arm compared with the SOCT arm included neurologic events (58% versus 17%, respectively). Subject incidence of TEAEs of interest with a difference ≥ 10% for subjects ≥ 65 years of age in the axicabtagene ciloleucel arm compared with the SOCT arm included neurologic events (65% versus 25%, respectively), hypogammaglobulinemia (20% versus 2%, respectively), and infections (61% versus 35%, respectively).

In the axicabtagene ciloleucel and SOCT arms, 106 and 120 subjects, respectively, were male and 64 and 48 subjects, respectively, were female. For both sexes, the percentage of subjects who experienced TEAEs and SAEs were generally similar (< 10% difference) between treatment arms. Subject incidence of TEAEs of interest with a difference ≥ 10% for male subjects in the axicabtagene ciloleucel arm or the SOCT arm included the neurologic events (58% versus 17%, respectively), hypogammaglobulinemia (10% versus 0, respectively), and infections (38% versus

28%, respectively). Subject incidence of TEAEs of interest with a difference ≥ 10% for female subjects in the axicabtagene ciloleucel arm or the SOCT arm included neurologic events (64% versus 27%, respectively), hypogammaglobulinemia (13% versus 2%, respectively), and infections (47% versus 35%, respectively).

In the axicabtagene ciloleucel and SOCT arms, 138 and 145 subjects, respectively, were White, 11 and 8 subjects, respectively, were Asian, 9 and 6 subjects, respectively, were Black or African American, and 12 and 9 subjects, respectively, were other races. For all races, the percentage of subjects who experienced TEAEs and SAEs were generally similar (< 10% difference) between the axicabtagene ciloleucel and SOCT arms, except that more SAEs were reported for Asian subjects (55% versus 38%, respectively) and Black or African American subjects (56% versus 17%, respectively), and treatment-related SAEs were also higher for Asian subjects (55% versus 38%, respectively), for Black or African American subjects (44% versus 17%, respectively), and for subjects of other races (25% versus 44%, respectively). Differences ≥ 10% in the incidence of certain AEs of special interest, such as neurologic events, hypogammaglobulinemia, and infections, were observed between treatment arms across all races; these results should be interpreted with caution due to small numbers.

Additional details are provided in m5.3.5.1, ZUMA-7 Primary Analysis CSR, Section 11.2.7.

The FDA's Assessment:

Axicabtagene ciloleucel arm:
A subgroup analysis for safety was conducted in subjects ≥65 years of age compared with <65 years of age. Out of the 168 subjects in the safety analysis population, 49 (29%) subjects were ≥65 years of age. Compared with subjects who were < 65 years old, subjects who were ≥ 65 years old showed a trend towards a higher incidence of SAEs (59% versus 46%), neurologic toxicity (80% versus 71%), ≥Grade 3 neurologic events (34% versus 21%), CRS (98% versus 90%) and ≥Grade 3 CRS (8% versus 6%).

There are insufficient data to evaluate safety according to race.

Reviewer comment:
In general, subjects ≥ 65 years old had a higher incidence of worst Grade 3 or higher AEs. Because of the small sample size of subjects aged 65 years and older who were treated in ZUMA-7, results should be interpreted with caution. The reviewer does not recommend including this observation in Section 8.5 "Geriatric Use" of the USPI.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were conducted to evaluate safety concerns.

The FDA's Assessment:

FDA agrees with Applicant's assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position

Secondary malignancies are a potential risk associated with axicabtagene ciloleucel. As of the data cutoff date (18 March 2021), no secondary malignancies were attributed to either axicabtagene ciloleucel or SOCT.

The FDA Assessment:

Secondary Malignancies - Axicabtagene Ciloleucel Arm:
Four secondary malignancies were identified: low grade spindle cell sarcoma (one subject) on treatment day 455, myelodysplastic syndrome (one subject) on treatment day 317, lung adenocarcinoma (one subject) on treatment day 456 and anal squamous cell carcinoma (one subject) on treatment day 557.

Subject ID (b) (6) 76 years old subject was diagnosed with Grade 1 follicular lymphoma, stage IV in 2017. Pre-treatment bone marrow biopsy demonstrated no dysplastic features. In February 2019, he developed transformed double hit large B-cell lymphoma and received six cycles of R-EPOCH and intrathecal methotrexate ending (b) (6). Disease progression occurred in end of June 2019. The subject was then randomized to the axicabtagene ciloleucel arm and was dosed on (b) (6). He achieved a complete response by Day 50 post-randomization and remains in CR. A bone marrow biopsy done 10 months post-treatment, on (b) (6) showed myelodysplastic syndrome with 1% blasts. Cytogenetics were complex karyotype (47,XY,+8[7]/45,XY,-7[5]/46,XY[8]). Anti-CD 19 CAR transgene analysis by PCR in bone marrow sample was negative. A peripheral blood sample collected at leukapheresis showed a precursor mutation for MDS (SRSF2 missense mutation) per (b) (4) report.

Reviewer comment:
The presence of precursor mutation for MDS at the time of leukapheresis and absence of anti-CD19 CAR transgene in the bone marrow biopsy indicates that this case of MDS is unlikely to be related to axicabtagene ciloleucel.

Standard of Care Arm:
Two treatment-emergent secondary malignancies were identified: metastatic malignant melanoma on treatment day 140 (in one subject) and transitional cell carcinoma on treatment day 322 .

Reviewer comment: None of the secondary malignancies are deemed related to the study treatment.

Axicabtagene ciloleucel Arm:

Cardiac toxicity:

Most common cardiac toxicity occurring at any grade included tachycardia (44%) and arrythmias (13%).

Table 52 includes all cardiac disorders and Table 53 includes details of the GT tachycardia and arrhythmia.

Table 52. FDA - All Reported Cardiac Disorders by Preferred Term or Grouped Preferred Term

Cardiac Disorders	Overall N = 168
	Grade 1-5 n (%)
Tachycardia*#	73 (44)
Arrhythmia*	22 (13)
Pericardial effusion	2 (1)
Cardiac aneurysm	1 (0.6)
Cardiac arrest	1 (0.6)
Cardiac failure	1 (0.6)
Cardiomyopathy	1 (0.6)
Myocardial infarction	1 (0.6)
Palpitations	1 (0.6)
Postural orthostatic tachycardia syndrome	1 (0.6)

Source: ADAEFDA Dataset
*Group term
#The following term includes events that occurred with CRS: tachycardia and arrhythmia. The event of cardiac failure and cardiomyopathy occurred in the setting of CRS.

Table 53. FDA - Tachycardia and Arrhythmia in Axicabtagene Ciloleucel Arm

Cardiac Disorders	Overall N = 146	
	Grade 1-5 n (%)	Grade 3-5 n (%)
Tachycardia*#	73 (43)	4 (2)
Sinus tachycardia	58 (35)	3 (2)
Tachycardia	15 (9)	1(0.6)
Arrhythmia*#	22 (13)	5 (3)
Atrial fibrillation	9(5)	5 (3)
Sinus bradycardia	6 (4)	0
Bradycardia	4 (2)	0
Ventricular tachycardia	3 (2)	0
Supraventricular extrasystoles	2 (0.6)	0
Arrhythmia	1 (0.6)	0
Extrasystoles	1 (0.6)	0
Supraventricular tachycardia	1 (0.6)	0
Ventricular extrasystoles	1 (0.6)	0

Source: ADAEFDA Dataset
*Group term
#The following terms includes events that occurred with CRS: tachycardia and arrhythmia.

Renal toxicity:

Renal insufficiency of any grade occurred in 19 subjects (11%) and Grade ≥3 in 4 (2%) subjects. One subject experienced vancomycin induced kidney injury that required renal dialysis.

Respiratory failure:

A total of three (5%) subjects developed respiratory failure and required endotracheal intubation and mechanical ventilation. An additional four subjects underwent mechanical ventilation for airway protection due to Grade 4 NT.

Concomitant procedures:

Concomitant procedures of interest included dialysis and ventilator support that occurred after the axicabtagene ciloleucel infusion. In total, eight subjects (5%) had procedures of interest, as follows:

- One subject underwent endotracheal intubation and mechanical ventilation from treatment day 10-18 for Grade 4 encephalopathy.
- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 7 for Grade 4 hypoxia and Grade 4 encephalopathy.
- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 6-10 for grade 4 encephalopathy.

- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 5-8 for Grade 4 hypoxia from CRS and Grade 4 encephalopathy.
- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 5-7 for Grade 4 acute respiratory failure from CRS and Grade 4 encephalopathy.
- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 4-8 for Grade 4 acute respiratory failure from CRS and Grade 4 encephalopathy.
- One subject underwent endotracheal intubation and mechanical ventilation on treatment day 5-11 for Grade 4 encephalopathy.
- One subject underwent dialysis for Grade 4 renal failure that was deemed related to antibiotic use (vancomycin related nephrotoxicity) used for treatment of bacteremia due to disease related complication of tumor bowel fistula.

Reviewer comment: Except for the renal failure, all other AEs that necessitated these procedures were deemed related to axicabtagene ciloleucel.

Hospitalization:

All 168 subjects in the safety analysis set who received axicabtagene ciloleucel were monitored at a health care facility for a minimum of 7 days. Axicabtagene ciloleucel was infused in an inpatient setting for 163 of 168 subjects. Five subjects (3%) received axicabtagene ciloleucel as planned outpatient infusions and all were subsequently hospitalized ; 3 subjects had same day elective admission to the hospital and 2 subjects had outpatient observation and were hospitalized within 7 days. All 168 subjects were eventually hospitalized. The median duration of hospitalization was 16 days. The observed range of the duration of hospitalization was 8-103 days. A total of 41 (24%) subjects were admitted to the intensive care unit (ICU). The median duration of ICU stay was 4.5 days with range of 1-12 days. The majority of subjects (36 or 88%) were admitted by Day 15.

120 -Day Safety Update:

The 120-Day safety update to the sBLA was submitted on 28 January 2022 under 125643/349/16 eSeq 0434, which included events that occurred in ZUMA-7 after the sBLA submission with data cutoff date of 26 August 2021. With this data cut off, subjects in ZUMA 7 have had the opportunity to be followed up for ≥21 months after their infusion of axicabtagene ciloleucel or their first dose of chemotherapy in SOC arm.

Between the data cut-off dates for the primary analysis and the 120-day safety analysis, an additional 6 subjects in the axicabtagene ciloleucel arm and 1 subject in the SOC arm had died.

Axicabtagene ciloleucel arm: Four deaths were from disease progression and occurred after initiation of subsequent therapy including transplantation and two deaths were from COVID 19.

One subject in the axicabtagene ciloleucel arm developed grade 3 hepatocellular carcinoma on treatment day 727 in the absence of known risk factors such as alcohol abuse, viral or autoimmune hepatitis. This AE was ongoing at the time of safety update.

SOC Arm: One death was due to disease progression and occurred after initiation of subsequent therapy.

One subject in the SOC arm developed Grade 2 Guillain-Barre syndrome on treatment day 543 in the absence of disease progression. The AE was ongoing at the time of safety update.

Reviewer comment:
The safety profile for axicabtagene ciloleucel remained consistent with what was observed in the original sBLA submission.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported in ZUMA-7.

The FDA's Assessment:
FDA reviewer agrees.

Pediatrics and Assessment of Effects on Growth (If Applicable)

The Applicant's Position:

Pediatric subjects were excluded from ZUMA-7.

The FDA's Assessment:
The ZUMA-7 study was limited to adult subjects 18 years of age and older.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

No change to the benefit-risk profile of axicabtagene ciloleucel is recommended following the most recent Periodic Safety Update Report, which reports postmarket safety assessments between 18 October 2020 and 17 April 2021.

As of 17 April 2021, 808 subjects have been exposed to axicabtagene ciloleucel in company sponsored interventional clinical studies. It is estimated that 4,497 patients have been exposed to axicabtagene ciloleucel in post-authorization use.

The FDA's Assessment:
No new safety issues were identified upon review of the most recent Periodic Safety Update Report.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

No new identified or potential risks for axicabtagene ciloleucel have emerged following the commercialization of this product and the overall benefit-risk evaluation for axicabtagene ciloleucel continues to be positive.

The FDA's Assessment:
REMS with ETASU will be implemented to ensure safe use in the post marketing setting.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

In the summary of clinical safety, the safety profile of axicabtagene ciloleucel in 170 subjects with r/r LBCL treated with axicabtagene ciloleucel in ZUMA-7 is compared with data from 108 subjects with r/r LBCL treated with axicabtagene ciloleucel in the supporting study, ZUMA-1 Phase 1 and Phase 2 (Cohorts 1 and 2). In addition, the safety profile of the pooled axicabtagene ciloleucel population (278 subjects) from ZUMA-7 and ZUMA-1 Phase 1 and Phase 2 (Cohorts 1 and 2) is compared with that of 168 subjects with r/r LBCL treated with SOCT in ZUMA-7. The results are briefly discussed herein. It should be noted that these studies were not designed to compare safety outcomes between studies; thus, results should be interpreted with caution.
Neurologic events in the supporting safety studies were identified by the Topp-based method and also identified via the system organ class search strategy (MedDRA search terms list that identifies neurologic events based on the MedDRA system organ classes of psychiatric disorders and nervous system disorders) (see Section 8.2.1); the results are provided in m5.3.5.3, ISS – System Organ Class Tables and Listings.

In general, the safety profile of axicabtagene ciloleucel as a second-line therapy observed in subjects with r/r LBCL in ZUMA-7 was consistent with the safety profile of axicabtagene ciloleucel as a third-line therapy observed in subjects with r/r LBCL in ZUMA-1. No new safety signals emerged. The identified risks, such as CRS and neurologic events, were manageable with medical intervention and generally resolved. Additional important identified risks associated with axicabtagene ciloleucel treatment include cytopenias, infections, and hypogammaglobulinemia, which were also manageable with antimicrobials and supportive care and generally resolved. Collectively, the data demonstrate a manageable safety profile of axicabtagene ciloleucel and support use of axicabtagene ciloleucel as a therapeutic option for the second-line treatment of r/r LBCL.

The results of the primary analysis of ZUMA-7 demonstrate that axicabtagene ciloleucel has a positive benefit-risk profile and is an important new therapeutic option for patients with

r/r LBCL.

The FDA's Assessment:

A comparative toxicity analysis between the two study arms was not conducted given that these are fundamentally different treatment strategies with innately different toxicity profile. In addition, toxicity data from SOC arm has limited utility since the safety population is markedly heterogenous in terms of treatment exposure; 10% of the subjects had received one cycle of chemotherapy, 54% had received two cycles of chemotherapy, 36% had received 3 cycles of chemotherapy and 37% had received 2-3 cycles of chemotherapy followed by HDT/HSCT. Finally, the toxicity profile of the SOC arm is already well characterized.

The safety analysis set for the axicabtagene ciloleucel arm included 168 subjects that received the conformal product. The most common non-laboratory adverse reactions (incidence ≥20%) included fever, CRS, fatigue, hypotension, encephalopathy, tachycardia, diarrhea, headache, musculoskeletal pain, nausea, febrile neutropenia, chills, cough, unspecified pathogen infection, dizziness, tremor, decreased appetite, edema, hypoxia, abdominal pain, aphasia and constipation. The most common (≥ 10%) Grade 3 or higher non-laboratory adverse reactions included febrile neutropenia, encephalopathy, and hypotension.

The most common (≥10%) Grade 3 or 4 laboratory abnormalities included leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia, hyponatremia and hyperglycemia. Serious adverse events (SAEs) occurred in 84 subjects (50%). The most common serious adverse reactions (> 5%) included CRS, fever, encephalopathy, hypotension, unspecified pathogen infection and pneumonia.

Three subjects had fatal adverse reactions: one with encephalopathy, one with progressive multifocal leukoencephalopathy (PML) and one with sepsis. One subject had Grade 4 NT ongoing at the time of death from disease progression.

Any grade of CRS occurred in 155 (92%) subjects, and neurologic toxicity occurred in 124 (74%) subjects. Most common Grade 3 or higher adverse events of special interest (AESI) included: prolonged cytopenias (56 subjects; 33%), febrile neutropenia (52 subjects; 31%), neurologic toxicities (NT) (42 subjects; 25%), infections (23 subjects; 14%), and CRS (11 subjects; 7%).

During conduct of the ZUMA-7 study, risk of life-threatening and fatal adverse reactions attributed to axicabtagene ciloleucel was mitigated by mandated site and investigator training, careful site selection and monitoring, and instructions for early detection and management of the most serious complications. The life-threatening and fatal adverse reactions warrant warnings, including a boxed warning for CRS and NT, and a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU). The USPI for axicabtagene ciloleucel already includes boxed warning for CRS and neurologic toxicity. The focus of the REMS ETASU is site preparation, patient education, and risk mitigation strategies with emphasis on early recognition and treatment of CRS and NT. To alert prescribers to clinically significant, serious, life-threatening and fatal adverse reactions associated with axicabtagene ciloleucel in the

current study, the following events from ZUMA -7 will be included in the Warnings and Precautions section of the label: CRS, NT, serious infections, prolonged cytopenias and hypogammaglobulinemia.

Because the most common toxicities were similar between Studies ZUMA-7, ZUMA-5 (the study that was the basis for approval of axicabtagene ciloleucel in r/r follicular lymphoma after two or more prior lines of therapy) and ZUMA -1 (the study that was the basis for approval of axicabtagene ciloleucel in r/r large B-cell lymphoma after two or more prior lines of therapy), the most common adverse reactions (non-laboratory and laboratory) will be presented, in the label, combined for all three studies.

The theoretical safety concerns include an increased risk of secondary malignancy due to replication-competent retrovirus (RCR) or insertional mutagenesis. There were no events of RCR infection or insertional mutagenesis reported in the sBLA.

Long-term safety after treatment with axicabtagene ciloleucel, particularly from the risk of insertional mutagenesis related secondary malignancies remains a concern due to the limited follow-up duration. The axicabtagene ciloleucel registry study which fulfills the ZUMA-1 post marketing requirement has completed the accrual goal of 1,500 DLBCL patients in October 2020. The ongoing follow up for 15 years will inform about the long-term toxicities in this population.

ISS datasets were not updated to reflect FDA's adjudication of CRS, NT and grouped terms for ZUMA -1. For example: the incidence of any grade CRS in the ISS ZUMA-1 is 93% (100/108) (refer Table 14.3.1.6.1, ISS) , however the original BLA review identified 101 subjects with CRS (94%). In addition, ZUMA-1 datasets do not include FDA's GTs. The analyses that the Applicant submitted in ISS to support the labeling changes were not considered as they were derived from the ZUMA-1 datasets that were not updated and therefore were inconsistent with current label. Therefore, ISS datasets were not used to generate the AESI that will be reflected in the label. Instead, the clinical review memos for ZUMA -1 and ZUMA-5 were used to generate the incidence of AEs and added to AEs from ZUMA -7; axicabtagene ciloleucel arm to summarize incidence of most frequent AEs in the Highlights Sections and incidence of AESI in Section 5 of the USPI.

The incidence of TEAEs that occurred in ≥20% of the safety population for all subjects in Cohort 1 and 2, ZUMA 1 (n=108), ZUMA 5 (n=146) and ZUMA-7; axicabtagene ciloleucel arm (n=168) combined is listed below in Table 54.

Table 54. FDA - Most common AEs in ZUMA-1, ZUMA-5 and ZUMA-7 Occurring in ≥30% of Safety Population (N=422)

TEAEs	ZUMA-1 N=108	ZUMA-5 N=146	ZUMA-7 N=168	ZUMA-1,ZUMA-5 Zuma-7 N=422
	Grade 1-5 %	Grade 1-5 %	Grade 1-5%	Grade 1-5 %
CRS	94	84	92	90
Fever	86	85	93	88
Hypotension	57	51	47	51
Encephalopathy	57	50	46	50
Tachycardia	57	44	43	47
Fatigue	46	49	52	49
Headache	45	45	41	43
Febrile neutropenia	34	41	31	37
Nausea	34	40	40	38
Infections with pathogen unspecified	26	42	25	31
Decreased appetite	44	26	24	30
Chills	40	29	28	31
Diarrhea	38	29	42	36
Musculoskeletal pain	14	40	40	33

Source: FDA Analysis

Adverse Events of Special Interest:
Incidences of CRS and neurologic toxicity AEs for ZUMA-1, Cohorts 1 and 2, (N=108 subjects), ZUMA-5 (N=146 subjects) and ZUMA-7 (N=168) combined are listed in Table 55. Table 55 also includes the most common symptoms of CRS and NT occurring in ≥10% of patients combined in ZUMA-1, ZUMA-5 and ZUMA-7. This information is included in Sections 5.1 and 5.2 of the USPI.

Table 56 includes Grade ≥3 infections, prolonged cytopenia, and hypogammaglobulinemia.

Serious CRS symptoms included cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure and hemophagocytic lymphohistiocytosis/macrophage activation syndrome Serious NT symptoms included aphasia, leukoencephalopathy, dysarthria, lethargy and seizures.

Table 55. FDA - Most Common AESIs for ZUMA-1, ZUMA-5 and ZUMA-7 (CRS and NT)

TEAEs	ZUMA-1 N=108		ZUMA-5 N=146		ZUMA-7 N=168		ZUMA-1,ZUMA-5 and ZUMA-7 N=422	
	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3
Subjects with any CRS, n(%)	101 (94)	14 (13)	123 (84)	11 (8)	155 (92)	11 (7)	379 (90)	36 (9)
CRS symptoms, % ^								
Fever (GT)	78		82		92		85	
Hypotension (GT)	41		36		42		40	
Tachycardia (GT)	28		29		38		32	
Hypoxia	22		21		18		20	
Chills	20		22		23		22	
Headache (GT)	12		14		19		15	
Fatigue (GT)	6		10		18		12	
Subjects with any NT, n(%)	94 (87)	34 (31)	112(77)	31 (21)	124 (74)	42 (25)	330 (78)	107 (25)
NT symptoms, % ^								
Encephalopathy* (GT)	57		50		46		50	
Headache (GT)	44		45		41		43	
Tremor	31		31		25		29	
Dizziness (GT)	21		20		21		21	
Aphasia*	18		14*		20		17	
Delirium (GT)	17		16		12		15	
Insomnia	9		13		9		10	

Note: Only relevant incidences pertinent to the label were included in this table.

*For ZUMA-5 analyses, the GT encephalopathy includes aphasia. Aphasia is counted twice under encephalopathy and aphasia.

^ For CRS and NT symptoms, the denominator is all patients in the safety population

Source: BLA 125643/0, sBLA 125643/248 and sBLA 125643/394.

Table 56. FDA - Most Common AESIs for ZUMA-1, ZUMA-5 and ZUMA-7 (Infections, Prolonged cytopenia and Hypogammaglobulinemia)

TEAE	ZUMA-1 N=108		ZUMA-5 N=146		ZUMA-7 N=168		ZUMA-1, ZUMA-5 and ZUMA-7 N=422	
	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3	Grade 1-5	Grade ≥3
Infections, n(%)	41 (38)	25(23)	78 (53)	23 (16)	73 (43)	23 (14)	192 (45)	71 (17)
Infections - pathogen unspecified, n(%)		17 (16)		21 (14)		13 (8)		51(12)
Bacterial infections, n(%)		10 (9)		3 (2)		8 (5)		21 (5)
Viral infections, n(%)		4 (4)		1 (0.7)		6 (4)		11 (3)
Fungal infections, n(%)		0		3 (2)		1 (0.6)		4 (0.9)
Febrile neutropenia, n(%)		42 (39)		60 (41)		52 (31)		154 (36)
Prolonged cytopenias by lab analysis, n(%)		51(47)		56 (38)		56(33)		163 (39)
Thrombocytopenia, %		25		10		8		13
Neutropenia, %		35		33		32		33
Anemia, %		17		5		5		8
Hypogammaglobulinemia as AE, n (%)	16 (15)	0	26 (18)	1	18 (11)	0	60(14)	0

Source: BLA 125643/0, s BLA 125643/248 and s BLA 125643/394 and Applicant IR Dated 2/28/2022

Reviewer comment:

1. Because the most common toxicities are similar in ZUMA-1, ZUMA-5 and ZUMA-7, these will be presented combined under Non-Hodgkin lymphoma (NHL) in the Highlights section of the label for all three studies.

2. Overall rate of CRS was similar across ZUMA-7 and ZUMA-1 (92% and 94%). The rate of ≥Grade 3 CRS was lower in ZUMA-7 compared to ZUMA-1 (7% and 13%). The difference in the rate of ≥Grade 3 CRS may be related to the difference in the study population and management of CRS across ZUMA-7 and ZUMA -1.

3. Overall rate of all grade NT (74% and 87%) and ≥Grade 3 NT (25% and 31%) was lower in ZUMA-7 compared to ZUMA -1. This difference may be related to the study population and management of NT across ZUMA-1 and ZUMA-7.

4. Prolonged cytopenia for the three studies ZUMA-1 , ZUMA-5 and ZUMA-7 are based on analysis of the ADLB dataset.

5. The incidence of hypogammaglobulinemia is likely higher given that it was based on adverse event reporting rather than analysis of laboratory datasets in the three studies.

6. It is noted that the rate of ≥Grade 3 infections, prolonged thrombocytopenia and anemia is lower in ZUMA-7 compared to ZUMA-1 (Refer to Table 56). This difference may be related to the more heavily pre-treated nature of the study population enrolled in ZUMA-1 compared to ZUMA-7.

Table 57. FDA - Grade 3 and 4 Laboratory Abnormalities in ≥30% of Safety Population in ZUMA-1, ZUMA-5 and ZUMA-7 (N=422)

Laboratory test	Grade 3-4 n (%)
Leukocytes decreased	401/422 (95)
Neutrophils decreased	391/421 (93)
Lymphocytes decreased	399/419 (95)
Hemoglobin decreased	180/422 (43)
Platelets decreased	156/422 (37)
Phosphorus decreased	92/253 (36)

Source: Applicant IR dated 2/28/2022. Based on number of patients having a baseline grade and at least one post-baseline grade for a given parameter.

Reviewer comment:
1. The most common Grade 3 and 4 laboratory abnormalities for three studies (ZUMA-1, ZUMA-5 and ZUMA-7) combined will be presented in the highlights section of the USPI. These are included in Table 57 above.
2. This analysis includes the subjects with both baseline grade and at least one post-baseline grade (evaluable) for each parameter and each study as the denominator.
3. Baseline was defined as the last value prior to or on the date of lymphodepleting chemotherapy as opposed to last lab value prior to axicabtagene ciloleucel infusion.
4. Updated analysis using the current definition of baseline (last value prior to or on the date of lymphodepleting chemotherapy) resulted in a significant increase in rate of Grade 3 and 4 lymphopenia in ZUMA-5 from 23% to 95%. Table 8 which includes Grade 3 or 4 laboratory abnormalities occurring in ≥10 % of patients in ZUMA-5 will be updated to reflect this analysis.

9 SUMMARY AND CONCLUSIONS

9.1. Statistical Issues

The FDA's Assessment:

1. The higher EFS event rate in the SOC arm compared to axicabtagene ciloleucel arm was driven primarily by the higher rate of NALT in the SOC arm. The events driven by NALT were further examined. The subset of NALT derived events included subjects that were ongoing responders per IRC but were considered as non-responders/PD per investigators, subjects with best response of SD per IRC after one cycle of chemotherapy and subjects who did not receive any protocol specified therapy post-randomization. These 32 events were excluded from a sensitivity analysis. Instead, these subjects were treated as responders and censored. Three additional events were also excluded from this sensitivity analysis: one subject who was inadvertently enrolled onto a different protocol after receipt of HDT and prior to receiving stem cell infusion, one subject with PR not taken for transplantation as institution required CR and one subject who attained PR but was not taken for transplantation and subsequently developed PD. The outcome of the sensitivity analysis was consistent with the primary analysis. EFS was significantly improved with axicabtagene ciloleucel compared to SOC with stratified hazard ratio of 0.7 (95% CI: 0.53, 0.92) and stratified log-rank two-sided p-value=0.0087. The outcome of this highly conservative sensitivity analysis shows that EFS results are robust.

2. PFS analysis shows that the axicabtagene ciloleucel arm had a higher proportion of PFS events: disease progression (46% vs. 42%) and deaths (6% vs. 3%) compared to SOC arm (Refer to Table 22). This is due to exclusion of NALT from the definition of PFS events and since the main difference in EFS events was driven by the higher rate of NALT in the SOC arm. However, the KM curve for PFS is superior for the axicabtagene ciloleucel arm (Refer to Figure 11) indicating that PFS events were delayed with axicabtagene ciloleucel compared to SOC. The median PFS was 14.9 mo (95% CI: 7.2, NE) with axicabtagene ciloleucel and 5 mo (95% CI: 3.4, 8.5) with SOC. 53.6% (95% CI: 45.8, 60.7) of subjects in axicabtagene ciloleucel arm were progression-free at 12 mo compared to 32.3% (95% CI: 23.5, 41.4) in the SOC arm indicating improved PFS with axicabtagene ciloleucel. Censoring in the axicabtagene ciloleucel arm was primarily due to ongoing responses and occurred in the later part of KM curve, whereas, censoring in the SOC arm was mostly due to NALT and occurred in the earlier part of KM curve.

9.2. Conclusions and Recommendations

The FDA's Assessment:

The primary evidence of effectiveness comes from Study ZUMA-7. This is a randomized, open-label, international, Phase 3 trial evaluating the efficacy of axicabtagene ciloleucel compared to second-line standard therapy in potentially transplant eligible subjects with relapsed/refractory

LBCL. Subjects with LBCL that were primary refractory or relapsed within 1 year of front-line chemoimmunotherapy were randomized in a 1:1 ratio to receive either a single infusion of axicabtagene ciloleucel at the approved dose following lymphodepleting chemotherapy or SOC. During manufacturing of axicabtagene ciloleucel, subjects could receive bridging corticosteroids at the discretion of the investigator. Standard therapy consisted of 2-3 cycles of a single, protocol-defined, investigator selected, platinum based chemoimmunotherapy. Subjects who responded to therapy per investigator assessment were to proceed to HDT followed by HSCT.

As of the 18 March, 2021 data cutoff, 359 subjects were randomized in the study; 180 subjects were randomized to the axicabtagene ciloleucel arm and 179 subjects were randomized to standard therapy. Compared to the standard therapy arm in which only 35% of the randomized subjects underwent transplantation, 94% of the randomized subjects in the axicabtagene ciloleucel arm underwent definitive treatment with CAR T cell infusion. The main reason for subjects randomized to the SOC arm to not proceed with HSCT was lack of response to chemotherapy.

The primary endpoint was EFS per the International Working Group Lugano Classification (Cheson 2014) as assessed by blinded central assessment in the ITT population. EFS was defined as 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 anti-lymphoma therapy, and death from any cause. The study met its primary objective by demonstrating that the risk of an EFS event in the axicabtagene ciloleucel arm is significantly reduced compared to the standard therapy arm with a stratified HR of 0.40 (95% CI: 0.31, 0.51), stratified log-rank p<0.0001. This translated into a longer median EFS in the axicabtagene ciloleucel arm compared to the standard therapy arm (8.3 mo and 2.0 mo). A higher estimated EFS rate at 18-month for axicabtagene ciloleucel arm relative to the standard therapy arm was observed (41.5 % {95% CI:34, 49} and 17% {95% CI:12, 23}). ORR per IRC in the axicabtagene ciloleucel arm was significantly improved compared to the standard therapy arm (83% {95% CI:77, 88} and 50% {95% CI: 43, 58}. The CR rate was higher in the axicabtagene ciloleucel arm compared to the standard therapy arm (65% {95% CI: 58, 72} and 32% {95% CI: 26, 40}. The PFS per IRC was improved in the axicabtagene ciloleucel arm compared to the standard therapy arm with a stratified HR of 0.56 (95% CI: 41, 76) with a longer median PFS at 15 mo (95% CI: 7.2, NE) in the axicabtagene ciloleucel arm compared to 5 mo (95% CI: 3, 9) in the standard therapy arm. A treatment effect was observed across all the subpopulations.

A planned interim analysis of OS was conducted at the time of primary efficacy analysis at 75% information fraction. While the difference in OS between the two arms is not statistically significant, the direction of the observed treatment effect is consistent with the EFS and PFS data. The OS results may be affected by the fact that 55% of the subjects in standard therapy arm received autologous CD19-directed CAR T therapy after experiencing an event.

This is concluded to be substantial evidence of effectiveness of axicabtagene ciloleucel for the treatment of adult subjects with primary refractory and early relapsed LBCL. The overall results of lower risk of an EFS event, higher ORR, CR rate with improved PFS in primary refractory and

early relapsed LBCL population indicates meaningful clinical benefit and justifies a regular approval for axicabtagene ciloleucel.

Safety analysis: The safety population for the axicabtagene ciloleucel arm included 168 subjects that received conformal product treated with one dose.
In summary:

- The most common non-laboratory adverse reactions (incidence ≥ 20%) included fever, cytokine release syndrome (CRS), fatigue, hypotension, encephalopathy, tachycardia, diarrhea, headache, musculoskeletal pain, nausea, febrile neutropenia, chills, cough, infection with pathogen unspecified, dizziness, tremor, decreased appetite, edema, hypoxia, abdominal pain, aphasia and constipation.
- The most comment Grade 3 or 4 laboratory abnormalities (incidence ≥10%) included: leukopenia (95%), neutropenia (94%), lymphopenia (94%), anemia (40%), thrombocytopenia (26%), hyponatremia (12%), hyperglycemia (11%).
- Grade 3 or higher adverse reactions occurred in 153 (91%) subjects.
- SAEs occurred in 84 (50%) subjects and included CRS, fever, encephalopathy, hypotension, unspecified pathogen infection and pneumonia.
- Three subjects had fatal adverse reactions: one with encephalopathy, one with progressive multifocal encephalopathy (PML), and one with sepsis. One subject had grade 4 encephalopathy ongoing at the time of death from disease progression.
- Most common Grade 3 or higher AESI included: prolonged cytopenias (56 subjects; 33%), febrile neutropenia (52 subjects; 31%), neurologic toxicities (42 subjects; 25%), infections (23 subjects; 14%), and CRS (11 subjects; 7%).
- Any grade CRS occurred in 155 (92%) subjects, and any grade neurologic toxicity occurred in 124 (74%) subjects.

No new safety signals were identified in this submission. CRS and neurologic toxicity associated with axicabtagene ciloleucel are serious, life-threatening and can be fatal. Treatment algorithms to mitigate these AEs as implemented in the study permit the benefits of treatment to outweigh these risks. None of the secondary malignancies during this study was attributed to the study product but concern for insertional mutagenesis and secondary malignancies remains.

Due to the lack of long-term safety data in the s BLA, a post marketing long-term follow-up registry study to fulfil the ZUMA-1 post-marketing requirement has completed enrollment of 1500 DLBCL patients. Follow up of patients for 15 years in this study will provide long-term safety data.

To enhance safety, the following measures should be followed:
• The product label includes a boxed warning for CRS and NT, and the warnings and precautions section conveys the treatment algorithm for CRS and NT management.
• Daily monitoring following axicabtagene ciloleucel infusion for 7 days.
• REMS with ETASU to assure the safe use of axicabtagene ciloleucel.

In summary, ZUMA-7 represents an adequate and well controlled study that provided substantial evidence of effectiveness in the context of an acceptable safety profile in support of regular approval.

The review team recommends 1) granting regular approval for axicabtagene ciloleucel for the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy, 2) Adding limitations of use statement: axicabtagene ciloleucel is not indicated for the treatment of patients with primary CNS lymphoma.

X X

Primary Clinical Reviewer Clinical Team Leader

10 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This application was not presented at an Advisory Committee meeting or to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

11 Pediatrics

The Applicant's Position:

Pediatric subjects have not been included in any study of axicabtagene ciloleucel.

The FDA's Assessment:
Reviewer agrees. In addition, axicabtagene ciloleucel was granted Orphan Drug Designation (ODD) on March 27, 2014 for the treatment of diffuse large B-cell lymphoma (DLBCL). Per PREA and 21 CFR 314.55(d), products with ODD are exempt from pediatric study requirements. Since this is a supplemental BLA, FDARA Title V which eliminates orphan exemption for pediatric studies for NME directed at relevant molecular targets does not apply. Therefore, submission of a pediatric assessment is not required for this submission.

12 Labeling Recommendations

The Applicant's Position:

Based on the high rates of durable responses observed in ZUMA-7 and the manageable safety profile of axicabtagene ciloleucel, the proposed therapeutic indication is for the treatment of patients with r/r LBCL. Additional recommendations are summarized in Table 58.

Table 58. Applicant - ZUMA-7 Labeling Recommendations

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.2 Indications and Usage, r/r LBCL	YESCARTA is indicated for the treatment of adult patients with r/r LBCL.	YESCARTA is indicated for adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.
5.1 Warnings and Precautions, CRS	Includes rates and severity of CRS observed in ZUMA-7 (Section 8.2.5 and m5.3.5.3 ISS Dataset Table 14.3.6.1 and Table 14.3.1.21).	Include rate, severity and duration of CRS observed following treatment with YESCARTA based on FDA's adjudication.
5.2 Warning and Precautions, Neurologic Toxicities	Includes rates and severity of neurologic toxicities observed in ZUMA-7 (Section 8.2.5 and m5.3.5.3 ISS Dataset Table 14.3.1.8.1 and Table 14.3.1.22).	Include rate, severity and duration of neurologic toxicities observed following treatment with YESCARTA based on FDA's adjudication
6.1 Clinical Trials Experience	Includes ADRs and laboratory abnormalities observed in ZUMA-7 (Section 8.2.4 and m2.5, Table 8).	Safety population in Yescarta arm includes 168 subjects who received the conformal product. This section includes ADRs, and laboratory abnormalities observed in ZUMA 7 based on FDA's adjudication of AEs, febrile neutropenia and FDA's grouped terms. Safety from standard therapy arm is excluded given that that the two treatment arms are innately different and the standard therapy arm is heterogenous in terms of treatment exposure. Therefore,

		comparative safety analysis has limited utility.
6.2 Immunogenicity	Includes immunogenicity based on ZUMA-7 (Section 8.2.5 and m2.7.4, Section 2.1.8.2).	Include immunogenicity based on the safety population in Yescarta arm in ZUMA-7.
12.3 Pharmacokinetics	Includes PK results based on ZUMA-7 (Section 6.2.1 amd PK/PD Report, Section 2.6.1.2).	Include PK results following treatment with Yescarta.
14.2 Clinical Studies, r/r LBCL	Includes efficacy data from ZUMA-7 (Section 8.1.2 and m2.7.3, Sections 1.2.1 and 2; CSR, Sections 8.2 and 8.4).	Efficacy data in this section was updated to: 1. Include 18-month EFS as opposed to 2-year EFS given the censoring pattern for ZUMA-7. 2. Statement comparing DOR between the two arms was removed as it is not an ITT analysis but a responder analysis. Instead, DOR data according to best overall response was added for Yescarta arm to inform prescribers that durability was driven by CR. 95% CI was added to the DOR as it is more informative metric than range. 3. Results from subgroup efficacy analyses were removed as these analyses are exploratory and at most hypothesis generating. 4. PFS as assessed by central review was included in the label as opposed to PFS assessed by investigator to be consistent with overall efficacy results that were based on central review. 5. Removed time from leukapheresis to product release as it is not informative to prescriber.

Abbreviations: ADR, adverse drug reactions; CRS, cytokine release syndrome; CSR, clinical study report; ISS, integrated summary of safety; FDA, Food and Drug Administration; LBCL, large B-cell lymphoma; PK, pharmacokinetic; r/r, relapsed/refractory.

The FDA's Assessment:

Negotiations between the OBE review team and the Applicant are ongoing at the time of this review. Refer to OBE review for details of the major REMS modification submissions.

The clinical review team recommends approval for the revised indication above. The rationale for the changes is as follows:

1. Characterization of the intended population: The Applicant has sought a broad indication statement for the treatment of patients with relapsed or refractory large B-cell lymphoma

which is not reflective of the population that was evaluated in ZUMA-7. ZUMA-7 enrolled a high-risk subset of r/r LBCL with primary refractory or relapsed disease within one year of first-line chemoimmunotherapy. Results from several studies such as CORAL, ORCHARRD, LY.25 and other retrospective data indicate that in addition to primary refractory disease, early relapse defined as either relapse within one year of diagnosis or attainment of CR or within one year of front-line chemoimmunotherapy confers poor outcome with salvage chemotherapy followed by HSCT compared to the later relapsed disease.

ZUMA-7 does not provide sufficient evidence to justify the use of axicabtagene ciloleucel in patients that relapse >12 months after completion of front-line therapy as these patients were excluded from the study. Patients with late relapses generally tend to be chemo-sensitive at the time of relapse and are a prognostically distinct subset of r/r LBCL. To merit an indication in a broad r/r LBCL which includes late relapses, the Applicant would need to explore the risk - benefit relationship of axicabtagene ciloleucel in such a study population preferably by a comparative trial.

During the study conduct, the eligibility criteria to define the timeframe of relapsed disease after CR was broadened to ≤12 months of either initiation or completion of first-line therapy as opposed to the originally proposed timeframe of ≤12 months of initiation of front-line therapy. Out of the 93 subjects that had best response of CR to front line therapy, 79 subjects (85%) had relapsed within 12 months of initiating front-line therapy and 13 subjects (14%) had relapsed > 12 months after initiating front line therapy and within 12 months of completing front line therapy. Review team discussed whether the indication statement should further define the timing of the relapse with respect to the front-line therapy. While early relapse is a well-known poor prognostic factor, it is defined variably and a unified definition of “early relapse” does not currently exist. For example, the CORAL study demonstrated that patients with relapse within 1 year of diagnosis have a poor outcome compared to relapse >1 year from diagnosis and the ORCHARRD study demonstrated that patients with CR duration of ≤12 months have worse outcome compared to CR duration of >12 months to frontline therapy. Since patients enrolled in ZUMA 7 had disease relapse defined from either initiation or completion of front line therapy and given the lack of a standard definition categorizing early relapse as poor risk, the review team recommended that the indication statement include adult patients with large B- cell lymphoma that is refractory to first- line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. This indication statement was felt to be most representative of the study population while providing greatest flexibility to the treating physician.

ZUMA-7 excluded patients with requirement of urgent therapy due to tumor mass effects such as bowel obstruction or blood vessel compression. The review team considers determination of need for urgent therapy, a matter of clinical judgement which should be decided by physicians in the practice of medicine. Therefore, this exclusion criteria for the study population is included in Section 14 of the label to inform prescribers as opposed to the indication statement.

Since ZUMA-7 limited enrollment to patients who were potentially candidates for HSCT, the risk

and benefit of axicabtagene ciloleucel is not established in patient who are not deemed to be transplant candidates. The review team considered an LOU or reflecting in the indication statement that the clinical benefit is not established in r/r LBCL patients who are "unfit" for autologous HSCT but ultimately favored describing the study population in Section 14.

2. Histological subtype in the indication statement: Primary mediastinal B cell lymphoma was excluded from study enrollment (See section 8.1.1;Inclusion/Exclusion criteria). Given that management of relapsed/refractory primary mediastinal B cell lymphoma is similar to other histological subsets of LBCL included in the study and since 8% of the efficacy population in ZUMA -1 had primary mediastinal B-cell lymphoma, we extrapolated the efficacy of axicabtagene ciloleucel in the second line setting to include this histology in the indication statement.

3 Limitation of use statement:
Patients with primary CNS lymphoma were ineligible for ZUMA-7. Hence, there is no clinical data addressing the efficacy or safety of axicabtagene ciloleucel in this population. Furthermore, there are concerns about the potential for adverse outcomes if NT were to develop in patients with pre-existent increased intracranial pressure and/or space occupying mass lesions within the brain. Therefore, we recommend a LOU statement that axicabtagene ciloleucel is not indicated for the treatment of patients with primary CNS lymphoma. This is similar to the LOU statement in place for the current indication statement for axicabtagene ciloleucel for r/r LBCL after two or more lines of systemic therapy.

4. ZUMA-7 was not designed to determine chemosensitivity of the study participants prior to randomization to the treatment arms and hence the superiority of axicabtagene ciloleucel compared to SOC in chemo-sensitive first relapse patients who are able to undergo transplantation is not determined. Furthermore, even in this high-risk disease setting, one-third of the subjects randomized to the SOC arm responded to chemotherapy and underwent HSCT. The exploratory analysis outlined in Section 8.1.1; Additional Analyses Conducted on the Individual Trial, indicates that in this selected subgroup of subjects (n=62), the outcome with median EFS of 12 months (95% CI: 8.5, NE) and 1-year EFS of 52% (95% CI: 38, 64) is at least comparable to the historical data for HSCT in the second-line setting (Refer to Table 1 in Section 2.2). HSCT continues to be a standard treatment option for these patients.The review team considered an LOU that efficacy of axicabtagene ciloleucel compared to HSCT has not been established in first chemo-sensitive relapse of LBCL. Since the decision to administer axicabtagene ciloleucel in the second line setting according to the new indication is made at the time of relapse prior to any treatment and determination of chemosensitivity, the addition of an LOU will not inform the safe and effective use. Hence, the review team decided to not incorporate an LOU in this regard.

13 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position

Because of the risk of CRS and neurologic toxicities, YESCARTA was approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use. With the REMS, hospitals and their associated clinics that dispense YESCARTA must be specially certified, and health care providers involved in the prescribing, dispensing, or administering of YESCARTA must be trained to recognize and manage CRS and nervous system toxicities.

At the Type B pre-s BLA meeting to discuss this s BLA (07 September 2021), the FDA agreed that a modification to the YESCARTA and TECARTUS REMS within the first 30 days of the s BLA submission (CRMTS #13506) is acceptable. With the approval of TECARTUS (STN: BL 125703/0), the YESCARTA REMS transitioned to the combined YESCARTA and TECARTUS REMS on 24 July 2020. As part of the combined REMS program, BLA 125703 was designated as the primary STN for all future submissions of the YESCARTA and TECARTUS REMS program using the trans-BLA process (STN: BL 125643/233). With the addition of the proposed indication of r/r LBCL, Kite will provide the draft REMS Major Modification in m1.16.2.2 of BLA 125703 for the combined YESCARTA and TECARTUS REMS. The REMS submission will include the REMS Document, REMS Supporting Document, REMS Educational Materials, and the Overview and Rationale including an impact assessment to the REMS with the addition of r/r LBCL to the label.

The FDA's Assessment:

Negotiations between the OBE review team and the Applicant are ongoing at the time of this review. Refer to OBE review for details of the major REMS modification submissions.

14 Postmarketing Requirements and Commitment

The FDA's Assessment:

The axicabtagene ciloleucel registry protocol KTE-C19-110 titled "Prospective, Long-term, Non-interventional, Cohort Study of Recipients of Axicabtagene Ciloleucel for Treatment of Relapsed or Refractory Large B-cell and Follicular Lymphoma" was originally submitted to BLA 125643 on 15 June 2018 to fulfill the ZUMA-1 post marketing requirement.

The primary objective of the study is to evaluate the development of subsequent neoplasms after administration of axicabtagene ciloleucel. The secondary objectives are to determine the rates of overall survival and causes of death, rate of relapse of primary malignancy, to evaluate the incidence and severity of CRS , neurologic toxicities, serious infections, prolonged cytopenias and hypogammaglobulinemia and to evaluate pregnancy outcomes. Patients with r/r LBCL are enrolled from 1 week prior to or up to 3 months after receiving axicabtagene ciloleucel infusion in the post-marketing setting and will be followed for 15 years. The accrual goal of 1,500 DLBCL patients for this study was completed in October 2020. This study will

provide long-term safety data in the r/r LBCL patients. In the absence of any new safety signals from ZUMA-7 in the second line r/r LBCL population, additional enrollment to the post marketing registry trial is not warranted.

15 Chief, Clinical Hematology Branch

X

16 Oncology Center of Excellence (OCE) Signatory

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

X

17 Division Director (DCEPT)

I concur with the clinical review team's/OCE's recommendation for approval of this efficacy supplement for YESCARTA for the treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. Substantial evidence of effectiveness and safety for this indication is based on a single adequate and well-controlled trial supported by the confirmatory evidence provided by existing adequate and well-controlled clinical trials that demonstrated the effectiveness of YESCARTA for the approved indication of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in diffuse large B-cell lymphoma.

X

18 Appendices

18.1. References

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18.2. Financial Disclosure

The Applicant's Position:

Financial disclosure forms were completed by investigators participating in ZUMA-7, in conformance with 21 CFR 54. The applicant identified 17 investigators who received significant payments of other sorts ≥ $25,000. Nine additional investigators self-disclosed financial interests and are included for transparency; however, Kite records indicate these investigators received significant payments of other sorts < $25,000. Three investigators did not sign financial disclosure forms, and certification of due diligence has been provided. Additional details are in m1.3.4 Financial Certification and Disclosure.

Kite has taken steps to minimize the potential bias of clinical study results by developing data handling procedures that maintain trial credibility and validity. The primary analysis of efficacy was based on a blinded central assessment of response. The evaluation of safety results, including AEs and laboratory results, were verified in source documents by the site monitor. Data handling procedures designed to maintain the trial credibility and validity in ZUMA-7 are detailed in the ZUMA-7 Statistical Analysis Plan. Through these measures, the financial interests of the investigators have minimal potential for introducing bias into the study results.

The FDA's Assessment:

The Applicant employed appropriate risk-reduction strategies to minimize bias and adequately investigated individuals who did not provide financial disclosure information. Neither the disclosed significant payments nor the missing disclosures are likely to have negatively impacted the integrity of ZUMA-7's conduct or findings. See Table 59 for details.

Table 59: ZUMA-7: Covered Clinical Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1090		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 26		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 26 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

18.3. Schedule of Assessments in ZUMA-7

Table 60. ZUMA-7: Schedule of Assessments: Axicabtagene Ciloleucel Arm

Procedures	Screening	Randomization	Leukapheresis	Conditioning Chemotherapy					IP Administration		Post Treatment Follow-up All Post Treatment visits are calculated from date of randomization		
Day	Within 14 days of randomization		Within approx. 5 days after randomization	d-5	d-4	d-3	d-2	d-1	Treatment d0	d1 – 7[m]	Day 50 (-7 to +21 days)	Day 100 (± 14 days)	Day 150 (± 14 days)
Medical history	X												
Physical exam[a]	X										X	X	X
Neurological assessment	X								X[n]	QOD[b]	X		
Weight (plus height at screening)	X		X										
Vital signs (BP, HR, RR, O2 sat, temp)	X		X								X	X	X
ECOG performance status	X												
ECG	X												
ECHO[o]	X												
PET-CT disease assessment[d]	PET-CT[q]										PET-CT	PET-CT	PET-CT
Archived tumor sample[e]	X[s]												
Pregnancy test (serum or urine)	X												X
Blood draw for chemistry panel	X		X	X					X	X	X	X	X
Blood draw for CBC w/differential	X		X	X					X	X	X	X	X
Blood draw for anti-axicabtagene ciloleucel antibodies[r]			X								X[r]		
Blood draw for LDH	X												
IXRS/Randomization call		X											
Lumbar Puncture[g]										X[g]			
Blood draw for CRP/Ferritin			X						X	X			
Blood draw for PBMCs and additional analysis[h]			X							d1, 3 & 7[h]	X[h]	X[h]	X[h]
Blood draw for cytokines[h]			X						X	d1, 3 & 7[h]	X[h]		X[h]
Blood draw for serology (EU sites)[t]	X[t]		X[t]										
EORTC QLQ-C30[i]	X			X					X		X	X	X
EQ-5D-5L[j]	X			X					X		X	X	X
WPAI[k]	X			X					X		X	X	X
Leukapheresis			X										
Fludarabine/Cyclophosphamide				X	X	X							
Axicabtagene ciloleucel infusion IV									X				
Adverse events/ Concomitant medication[c]	X		X	X	X	X	X	X	X	X	X	X	X

Table 61. ZUMA-7: Schedule of Assessments: SOC Arm

Procedures	Screening	Randomization	Treatment Period Cycle 1 and Cycle 2		Disease Assessment calculated from date of randomization	Treatment Period HDT-ASCT or Cycle 3–HDT-ASCT (optional)	Post Treatment visits are calculated from date of randomization	
							Post HDT-ASCT	Post Tx FU
Day	Within 14 days of randomization		Cycle 1 Within approx. 5 days after randomization	Cycle 2	Day 50 (-7 to +21 days)	HDT-ASCT or Cycle 3-HDT-ASCT	D100 (± 14 days)	Day 150 (± 14 days)
Medical history	X							
Physical exam[a]	X				X		X	X
Neurological assessment	X				X			
Weight (plus height at screening)	X							
Vital signs (BP, HR, RR, O2 sat, temp)	X				X		X	X
ECOG performance status	X							
ECG	X							
ECHO[b]	X							
PET-CT disease assessment[c]	PET-CT[b]				PET-CT		PET-CT	PET-CT
Archived tumor sample[d]	X							
Pregnancy test (serum or urine)	X							X
Blood draw for chemistry panel	X		X	X	X	X	X	X
Blood draw for CBC w/differential	X		X	X	X	X	X	X
Blood draw for LDH	X							
Blood draw for additional analysis[d]			X		X		X	X
IXRS / Randomization call		X						
EORTC QLQ-C30[e]	X		X		X	day of transplant	X	X
EQ-5D-5L[e]	X		X		X	day of transplant	X	X
WPAI[e]	X		X		X	day of transplant	X	X
SOC chemotherapy[f]			X	X		X (Cycle 3 is optional)		
Leukapheresis[g]						X[g]		
HDT[g]						X[g]		
CD34+ stem cell infusion[g]						X[g]		
Adverse events[h]/ Concomitant medication[i]	X		X	X	X	X	X	X

Table 62. ZUMA-7: Schedule of Assessments: Long-term Follow-up

Procedure	Long-term Follow-up Period 1 Each visit calculated from randomization (all visits have ± 28 day window)											
Visit frequency	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60
Physical exam[a]	X	X	X	X	X	X						
PET-CT scan/CT Scan disease assessment[b]	PET-CT	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]	PET-CT/CT[b]
Survival status	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential[c]	X	X	X	X	X	X						
Blood draw for PBMCs and additional analysis[d]	X	X		X		X		X		X		X
Targeted SAEs[e]	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL[f]	X	X	X	X	X	X	X	X	X	X	X	X
PROs[g]	X	X	X	X	X	X						

18.4. FDA Grouped Terms

Grouped terms that were used for FDA analyses of adverse events are listed in Table 63 below.

Table 63. FDA - Grouped Terms Used for FDA Analyses of Adverse Events

FDA Grouped Terms	Preferred Terms
Abdominal pain	Abdominal discomfort
	Abdominal pain
	Abdominal pain lower
	Abdominal pain upper
	Dyspepsia
Affective disorder	Anxiety
	Depression
	Mood altered
Arrhythmia	Arrhythmia
	Atrial fibrillation
	Bradycardia
	Electrocardiogram QT prolonged
	Extrasystoles
	Sinus bradycardia
	Supraventricular extrasystoles
	Supraventricular tachycardia
	Ventricular extrasystoles
	Ventricular tachycardia
Ataxia	Ataxia
	Co-ordination abnormal
	Gait disturbance
	Vestibular disorder
Clostridium difficile infection	Clostridium difficile colitis
	Clostridium difficile infection
Coagulopathy	Blood fibrinogen decreased
	Coagulopathy
	International normalized ratio increased
	Hypofibrinogenemia
	Prothrombin level decreased
Cough	Cough
	Productive cough
	Upper-airway cough syndrome
Delirium	Agitation
	Hallucination
	Irritability

FDA Grouped Terms	Preferred Terms
	Restlessness
	Delirium
	Delusion
	Disorientation
Diarrhea	Colitis
	Diarrhoea
Dizziness	Dizziness
	Dizziness postural
	Presyncope
	Syncope
	Vertigo
Dyspnea	Dyspnoea
	Dyspnoea exertional
Edema	Face oedema
	Fluid overload
	Generalized oedema
	Hypervolaemia
	Localised oedema
	Oedema
	Oedema genital
	Oedema peripheral
	Periorbital oedema
	Peripheral swelling
	Pulmonary oedema
Encephalopathy	Altered state of consciousness
	Amnesia
	Apraxia
	Bradyphrenia
	Cognitive disorder
	Confusional state
	Depressed level of consciousness
	Disturbance in attention
	Dysarthria
	Dysgraphia
	Dyspraxia
	Encephalopathy
	Lethargy
	Loss of consciousness
	Memory impairment
	Mental impairment

FDA Grouped Terms	Preferred Terms
	Mental status changes
	Metabolic encephalopathy
	Slow speech
	Somnolence
	Toxic encephalopathy
Facial paralysis	Facial asymmetry
	Facial nerve disorder
	Facial paralysis
	Facial paresis
Fatigue	Asthenia
	Fatigue
	Malaise
Fever	Pyrexia
Headache	Headache
	Tension headache
Hemorrhage	Epistaxis
	Gastric haemorrhage
	Haematemesis
	Haematochezia
	Haematoma
	Haematuria
	Haemorrhage intracranial
	Haemorrhage urinary tract
	Haemorrhoidal haemorrhage
Hypotension	Capillary leak syndrome
	Hypotension
	Orthostatic hypotension
Insomnia	Insomnia
	Sleep deficit
Motor dysfunction	Muscle contractions involuntary
	Muscle spasms
	Muscle twitching
	Muscular weakness
Musculoskeletal pain	Arthralgia
	Arthritis
	Back pain
	Bone pain
	Flank pain
	Groin pain
	Musculoskeletal pain

FDA Grouped Terms	Preferred Terms
	Musculoskeletal chest pain
	Myalgia
	Neck pain
	Non-cardiac chest pain
	Pain in extremity
Neuropathy peripheral	Hypoaesthesia
	Lumbar radiculopathy
	Neuropathy peripheral
	Paraesthesia
	Peroneal nerve palsy
	Sciatica
Paresis	Hemiparesis
	Moniparesis
Pneumonia	Lung infiltration
	Pneumocystis jirovecii pneumonia
	Pnuemonia aspiration
	Pneumonia
	Pneumonia staphylococcal
Rash	Dermatitis
	Dermatitis allergic
	Dermatitis bullous
	Drug eruption
	Erythema
	Pruritus
	Rash
	Rash macular
	Rash maculo-papular
	Rash pruritic
	Urticaria
Renal insufficiency	Acute kidney injury
	Blood creatinine increased
	Chronic kidney disease
Respiratory failure	Acute respiratory failure
	Respiratory failure
Sepsis	Bacteraemia
	Clostridium bacteraemia
	Enterobacter bacteraemia
	Klebsiella bacteraemia
	Pseudomonal sepsis
	Sepsis

FDA Grouped Terms	Preferred Terms
	Urosepsis
Tachycardia	Sinus tachycardia
	Tachycardia
Thrombosis	Axillary vein thrombosis
	Brachiocephalic vein thrombosis
	Deep vein thrombosis
	Embolism
	Jugular vein thrombosis
	Pulmonary embolism
	Thrombosis
Visual Impairment	Vision blurred
	Visual impairment

Source: FDA Analysis. ADAEFDA

Table 64. FDA - All CRS Symptoms in ZUMA-7

CRS Symptoms/AEs	All grade AE, n (%) N=168	Grade ≥3 AE, n(%) N=168
Total	155 (92%)	51 (30%)
Fever (GT)	154 (92%)	14 (8%)
Hypotension (GT)	70 (42%)	18 (11%)
Tachycardia (GT)	64 (38%)	4 (2%)
Chills	38 (23%)	0
Headache (GT)	32 (19%)	2 (1%)
Fatigue (GT)	31 (18%)	4 (2%)
Hypoxia	30 (18%)	12 (7%)
Nausea	17 (10%)	2 (1%)
Transaminases increased (GT)	16 (10%)	2 (1%)
Diarrhea (GT)	14 (8%)	1(0.6%)
Musculoskeletal pain (GT)	13 (8%)	0

CRS Symptoms/AEs	All grade AE, n (%) N=168	Grade ≥3 AE, n(%) N=168
Vomiting	11 (7%)	0
Arrhythmia (GT)	10 (6%)	4 (2%)
Decreased appetite (GT)	9 (5%)	3 (2%)
Renal insufficiency (GT)	6 (4%)	0
Tachypnea (GT)	5 (3%)	1(0.6%)
C-reactive protein increased	4 (2%)	1(0.6%)
Blood alkaline phosphatase increased	3 (2%)	0
Dyspnea (GT)	3 (2%)	2 (1%)
Edema (GT)	3 (2%)	1(0.6%)
Rash (GT)	3 (2%)	0
Hyperbilirubinemia (GT)	2 (1%)	0
Hypertension	2 (1%)	1(0.6%)
Hypophosphatemia (GT)	2 (1%)	0
Influenza like illness	2 (1%)	0
Respiratory failure (GT)	2 (1%)	2 (1%)
Apnea	1 (0.6%)	1 (0.6%)
Cardiac failure (GT)	1 (0.6%)	1 (0.6%)
Cardiomyopathy	1 (0.6%)	1 (0.6%)
Coagulopathy (GT)	1 (0.6%)	1 (0.6%)
Cough (GT)	1 (0.6%)	0
Dizziness (GT)	1 (0.6%)	0
Hypomagnesemia	1 (0.6%)	0
Hyponatremia	1 (0.6%)	1 (0.6%)

CRS Symptoms/AEs	All grade AE, n (%) N=168	Grade ≥3 AE, n(%) N=168
Hypothermia	1 (0.6%)	0
Pleural effusion	1 (0.6%)	1 (0.6%)
Serum ferritin increased	1 (0.6%)	0
Shock (GT)	1 (0.6%)	0
Tremor	1 (0.6%)	1 (0.6%)
Troponin increased (GT)	1 (0.6%)	0
Urinary incontinence	1 (0.6%)	0
Visual impairment (GT)	1 (0.6%)	0

Source: ADAEFDA Dataset