CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-12)
Protocol Number:	KTE-C19-112
Indication:	First-line treatment of adult subjects with high-risk large B-cell lymphoma, including either high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* translocations, or large B-cell lymphoma with a high intermediate/high risk International Prognostic Index (IPI) score of ≥ 3; all subjects must have positive positron emission tomography after 2 cycles (PET2+) of chemoimmunotherapy.
Kite Investigational Product:	Axicabtagene ciloleucel
Company Code:	KTE-C19
IND Number:	016278
EudraCT Number:	2019-002291-13
Clinical Trials.gov Identifier:	NCT03761056
Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404
Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List.
Original Protocol Date:	26 June 2018
Amendment 1:	14 August 2019
Amendment 2:	25 March 2022
Amendment 3:	14 June 2022

CONFIDENTIALITY NOTICE

Sponsor and Investigator Signature Page

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STUDY ACKNOWLEDGMENT

A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-12)

Amendment 3.0, 14 June 2022

This protocol has been approved by Kite Pharma, Inc. The following signature documents this approval.

PPD

Kite Medical Monitor Name (Printed)

15-Jun-2022

Date

PPD

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kite Pharma, Inc. I will discuss this material with them to ensure that they are fully informed about the investigational product and study.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner, and dependent children)
- Sub investigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

Principal Investigator Name (Printed)

Signature

Date

Study Site Number

PROTOCOL SYNOPSIS

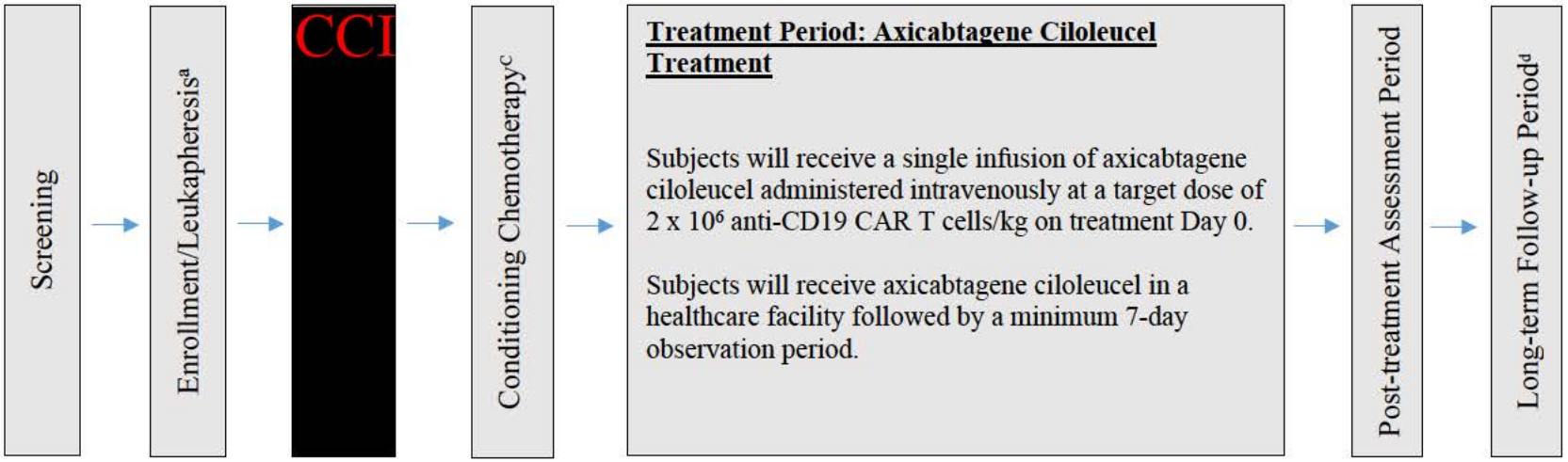
Title:	A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-12)
Indication:	The indication is for the first-line treatment of adult subjects with high-risk large B-cell lymphoma, including either high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* translocations (hereafter referred to as double-hit or triple-hit lymphomas), or large B-cell lymphoma with a high intermediate/ high risk International Prognostic Index [IPI] score of ≥ 3; all subjects must have positive positron emission tomography after 2 cycles (PET2+) of chemoimmunotherapy.
Study Design:	Approximately 40 subjects with high-risk large B-cell lymphoma (either double-/triple-hit lymphomas, or high-risk large B-cell lymphoma with IPI score ≥3) will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg body weight. Each subject with a positive interim positron emission tomography-computed tomography (PET-CT) per the Lugano Classification {Cheson 2014} (Deauville 5-point scale PET score of 4 or 5) after 2 cycles (PET2+) of chemoimmunotherapy will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • CCI [redacted] • Conditioning chemotherapy period • Investigational product treatment period • Post-treatment assessment period • Long-term follow-up (LTFU) period Following at least 36 months of assessments, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in the separate LTFU study, KT-US-982-5968. For study requirements assigned to each study period, refer to Section 7 for details. A study schema is provided at the end of the protocol synopsis section.

Study Objectives:	The primary objective of the study is to estimate the efficacy of axicabtagene ciloleucel, as measured by complete response (CR) rate, in subjects with high-risk large B-cell lymphoma. Secondary objectives will include assessing the safety of axicabtagene ciloleucel and additional efficacy endpoints.
Hypothesis:	No formal hypothesis will be tested in this study. The study is designed to estimate the CR rate in subjects with high-risk large B-cell lymphoma treated with axicabtagene ciloleucel as first-line therapy.
Primary Endpoints:	CR rate: CR rate is defined as the incidence of a CR per the Lugano Classification {Cheson 2014} as determined by study investigators. All evaluable subjects who do not meet the criteria for a CR by the analysis data cutoff date will be considered nonresponders.
Secondary Endpoints:	• Objective response rate (ORR): ORR is defined as the incidence of either a CR or a partial response per the Lugano Classification {Cheson 2014} as determined by study investigators • Duration of response (DOR) • Event-free survival (EFS) • Progression-free survival (PFS) • Overall survival (OS) • Incidence of adverse events (AEs) and clinical significant changes in safety laboratory values • Relapse with central nervous system (CNS) disease Additional Secondary Endpoints: • Pharmacokinetics (levels of anti-CD19 CAR T cells in blood) • Pharmacodynamics (levels of cytokines in serum)
Sample Size:	Approximately 40 enrolled and treated subjects
Study Eligibility:	Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria.

Treatment:	Investigational Product: • Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing ≥ 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered. CCI [redacted]
Procedures:	At specific time points as outlined in the schedule of assessments, subjects will undergo the following assessments/procedures: collection of informed consent, general medical history including previous treatments for large B-cell lymphoma, physical exam including vital signs and Eastern Cooperative Oncology Group performance status, neurologic examinations, blood draws for complete blood count, chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, replication-competent retrovirus and anti-CD19 CAR T-cell analysis. Subjects will also undergo a baseline electrocardiogram, echocardiogram, PET-CT, and leukapheresis. Subjects may also need bone marrow aspirate/biopsy, brain magnetic resonance image, and lumbar puncture. Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and AEs and will have their disease assessed.

Data Safety Monitoring Board:	An independent Data Safety Monitoring Board (DSMB) will be chartered to meet and review the serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) on a semi-annual basis after the first subject has been treated with axicabtagene ciloleucel up through the primary analysis. Kite Pharma, Inc., or delegate, will submit SAEs and SUSARs to the DSMB on a regular basis throughout the study up through the primary analysis. The DSMB will also meet to review safety data after 15 subjects have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 3 months after axicabtagene ciloleucel infusion. The DSMB will make trial conduct recommendations on an ongoing basis based on an analysis of risk versus benefit. The DSMB may request additional safety data for review or recommend modifications to the study conduct if safety concerns are identified. The DSMB may meet more often as needed. Refer to Section 9.10.
Statistical Considerations:	No formal hypothesis test will be performed. Analyses will be descriptive. One planned interim analysis will be performed. • Interim Analysis 1 will be conducted after 15 subjects have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 3 months after axicabtagene ciloleucel infusion. This analysis will be for efficacy and safety. The primary endpoint for the study is CR rate per the Lugano Classification {Cheson 2014} as determined by study investigators. The primary analysis will occur after all subjects treated with axicabtagene ciloleucel have an opportunity to be assessed for response 6 months after the Week 4 disease assessment. The final analysis will occur when all subjects have had the opportunity to be followed for at least 36 months. Subjects treated with axicabtagene ciloleucel will be transitioned to the KT-US-982-5968 study for the remainder of the 15-year LTFU period. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

Figure 1. Study Schema



Approximately 40 subjects who are either double hit/triple hit or have IPI ≥ 3 will be enrolled and treated.

[a] **Enrollment/Leukapheresis:** Subjects who have a positive interim PET per the Lugano Classification {Cheson 2014} (Deauville PET score of 4 or 5) after 2 cycles (PET2+) of an anti-CD20 monoclonal antibody and anthracycline-containing regimen per local standard of care (eg, DA-EPOCH-R) if double hit/triple hit, or an anti-CD20 monoclonal antibody and anthracycline-containing regimen per local standard of care (eg, R-CHOP) if large B-cell lymphoma with IPI score ≥ 3.

[b] CCI

[c] **Conditioning Chemotherapy:** Subjects will receive a 3-day conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day (Day –5 to Day –3) followed by 2 rest days (Day –2 and Day –1).

[d] **Long-term Follow-up Period:** After the end of ZUMA-12, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate long-term follow-up study, KT-US-982-5968.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5PS	5-point scale
ABC	activated B-cell
AE	adverse event
BP	blood pressure
CAR	chimeric antigen receptor
CBC	complete blood count
CD	cluster of differentiation
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DA-EPOCH-R	dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab
DH	double-hit
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DORR	duration of retreatment response
DSMB	Data Safety Monitoring Board
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCB	germinal center B-cell
GCP	Good Clinical Practice
GELA	Groupe d'Etude des Lymphomes de l'Adulte
HIV	human immunodeficiency virus
HDMP	high-dose methylprednisolone
HEENT	head, eyes, ears, nose, and throat
HGBL	high-grade B-cell lymphoma
HR	heart rate

IB	Investigator's Brochure
ID	identification
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
IPI	International Prognostic Index
IPM	investigational product manual
IRB	institutional review board
IRC	independent review committee
IV	intravenous
IWG	international working group
LDi	longest transverse diameter
LTFU	long-term follow-up
MCP	monocyte chemoattractant protein
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PK	pharmacokinetic
PMBCL	primary mediastinal B-cell lymphoma
PMD	progressive metabolic disease
PR	partial response
PFS	progression-free survival
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R-ACVBP	rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone
RCR	replication-competent retrovirus
SAE	serious adverse event
SCT	stem cell transplant
SDi	shortest transverse diameter
SOA	schedule of assessments
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

- To estimate the efficacy of axicabtagene ciloleucel, as measured by complete response (CR) rate, in subjects with high-risk large B-cell lymphoma, as determined by study investigators

1.2. Secondary Objective(s)

- To characterize the safety profile, and to further characterize efficacy with secondary endpoints; further secondary objectives will include pharmacokinetic/pharmacodynamic endpoints

1.3. CCI [redacted]

- To investigate CCI [redacted] product

2. DISEASE BACKGROUND

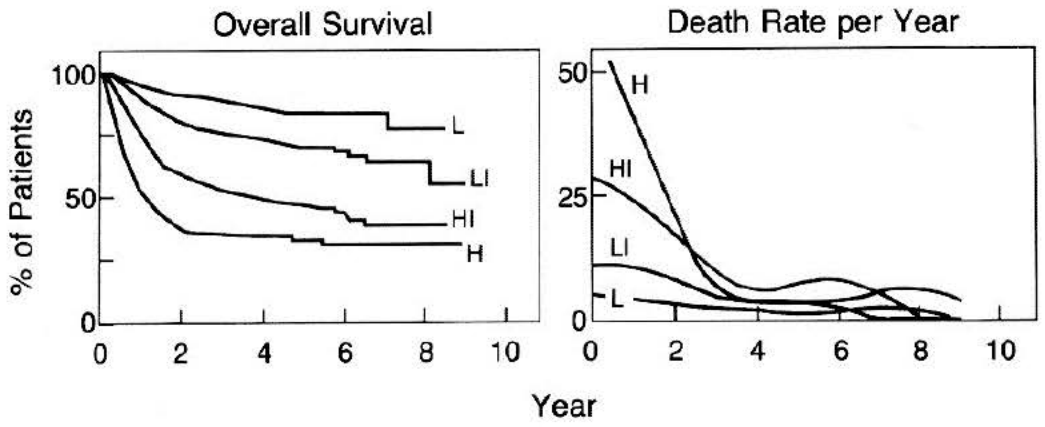
2.1. Disease Background

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 among men and women, accounting for 4% of all new cancer cases and 3% of cancer-related deaths {Howlader 2015}. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of B-cell NHL, accounting for approximately 30% to 40% of all cases across regions {Chaganti 2016, Morton 2006, Sehn 2015, Tilly 2012}. DLBCL can be further divided into subtypes based on factors including cytology, site of origin, and clinical background. Nevertheless, most cases are classified as DLBCL-not otherwise specified (NOS). The 2016 revision of the World Health Organization (WHO) classification of lymphomas included 2 new subcategories of DLBCL-NOS by cell of origin: activated B-cell (ABC) and germinal center B-cell (GCB). Per the new classification system, DLBCL-NOS also includes those with MYC or BCL-2 protein overexpression, which has been suggested to confer worse outcome in patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line therapy {Swerdlow 2016}.

The 2016 revision of the WHO classification for lymphomas also included a new category, high-grade B-cell lymph oma (HGBL), which accounts for < 10% of DLBCL cases and is now considered distinct from DLBCL {Friedberg 2017, Swerdlow 2016}. HGBL includes 2 subcategories, the first of which is characterized by gene rearrangements of *MYC* and *BCL-2* and/or *BCL-6* (ie, double- or triple-hit lymphomas, depending on the number of rearrangements present). The second category lacks these rearrangements and is characterized by the presence of Ki67 protein (HGBL-NOS) {Broyde 2009, Swerdlow 2016}. Double- and triple-hit lymphomas typically do not respond to rituximab-based chemoimmunotherapy and are more likely to involve the central nervous system (CNS) {Friedberg 2017}. Only 40% and 41% of patients with *MYC* translocations and with double-hit lymphoma, respectively, were alive 2 years following first-line treatment {de Jonge 2016, Oki 2014}. Retrospective studies suggest a benefit of aggressive induction regimens, and consideration is even given for consolidation with high-dose therapy and transplant in select cases {Chen 2017, Friedberg 2017}.

The International Prognostic Index (IPI) is widely used for risk stratification of patients with aggressive B-cell lymphoma. In the original study of 2031 patients of all ages, the prognostic model, based on age, tumor stage, serum lactate dehydrogenase concentration, performance status, and number of extranodal disease sites, identified 4 risk groups of low, low-intermediate, high-intermediate, and high with predicted 5-year survival rates of 73%, 51%, 43%, and 26%, respectively {International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993} (Figure 2). The IPI also remains a valid predictor of outcome in the rituximab era, independent of double-hit status and cell of origin (eg, GCB and ABC subtypes) {Staiger 2017, Ziepert 2010}.

Figure 2. International Prognostic Index in Aggressive Lymphomas



Prognostic factors: age > 60 years; performance status ≥ 2; lactate dehydrogenase > 1 x normal; extranodal sites > 1; Stage III or IV
Risk category (number of factors): Low (L: 0 or 1) l Low-intermediate (LI; 2); High-intermediate (HI; 3); High (H; 4 or 5)
[International NHL Prognostic Factors Project. N Engl J Med. 1993;329:987-94]

A number of recent studies have assessed the role of early PET-CT using visual analysis by Deauville criteria {Barrington 2014} to further predict patients with large B-cell lymphoma treated with rituximab-containing regimens who may be at higher risk. An international retrospective confirmatory study reported that early positive PET-CT after 2 induction cycles (PET2+) had prognostic value in DLBCL when there is no change in therapy: the 3-year PFS estimate was 59% in PET2+ patients versus 81% in PET2-negative (PET2−) patients (P = 0.003) {Itti 2013}. A meta-analysis of 11 studies revealed higher CR rates in the early (after 2 to 4 induction cycles) PET-negative group compared with the early PET-positive group (relative risk: 5.5, 95% confidence interval [CI]: 2.59 to 11.80) {Zhu 2015}. A prospective study in DLBCL patients assessed PET2 by central review, and found a 2-year EFS rate of 48% for PET2+ patients and 74% for PET2− patients (P = 0.004) {Mamot 2015}. Another prospective study in DLBCL patients revealed PET2 results to be prognostic for PFS based on cell of origin, with a 30-month PFS of 60% for PET2+ patients vs. 100% for PET2− patients with GCB DLBCL (P = 0.001) {de Oliveira Costa 2016}. Based on the results of these studies, patients with large B-cell lymphoma who are PET2+ based on Deauville criteria appear to have a worse prognosis compared with patients who are PET2− and represent a subgroup with a high unmet medical need.

This study will enroll patients with high-risk large B-cell lymphoma, defined as either double-/triple-hit lymphoma or large B-cell lymphoma with high-intermediate and high risk (IPI ≥ 3). All study subjects must also be PET2+. Given the poor outcomes observed with currently available therapies, this group has a high need for more effective treatment.

2.2. Standard First-line Therapy

Since the 1970s, chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) had been standard-of-care first-line therapy for patients with DLBCL. More intensive combinations failed to show additional survival benefit. The current standard of care for first-line treatment is CHOP in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP, rituximab-based chemoimmunotherapy) {Flowers 2010}. In the seminal study by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), first-line R-CHOP was superior to CHOP, with 10-year overall survival (OS) and progression-free survival (PFS) of 43.5% vs 27.6% and 36.5% vs 20.1%, respectively {Coiffier 2010}. Thus, while more effective than chemotherapy alone, first-line R-CHOP still only results in long-term disease remission in < 40% of subjects. Recently a Phase 3 trial of first-line R-CHOP versus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) demonstrated no difference in event-free survival (EFS) or OS between the regimens {Wilson 2016}.

Patients with double- and triple-hit lymphomas have been shown to have a poor prognosis with R-CHOP chemoimmunotherapy, and there is no established standard of care {Green 2012, NCCN 2016}. In a large retrospective study of patients with double-hit lymphoma, there was no apparent benefit with the more aggressive induction regimen DA-EPOCH-R, compared with standard R-CHOP, with a median OS of 30 months and 34 months, respectively {Petrich 2014}. In the GELA randomized Phase 2 study, which evaluated the efficacy of rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) or R-CHOP-14 induction using IWG (International Working Group) 2007 criteria in young patients with high-risk DLBCL, the primary objective of achieving a higher than 50% CR rate after 4 cycles of induction regimen was not met in either randomization group {Casasnovas 2017}.

Unfortunately, there are no published prospective trials in the setting of double- or triple-hit lymphoma. These patients represent the greatest unmet clinical need in DLBCL according to a recent clinical trials planning meeting from the National Cancer Institute National Clinical Trials Network, and prospective randomized trials are currently being developed for double-hit lymphoma {Nowakowski 2016}.

2.3. Axicabtagene Ciloleucel

On 18 October 2017, the Food and Drug Administration (FDA) granted regulatory approval to axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL-NOS, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma {YESCARTA 2019}.

Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell immunotherapy. It consists of autologous T cells that are genetically modified to produce a CAR protein, allowing the T cells to identify and eliminate CD19-expressing normal and malignant cells. CD19 is expressed by most B-cell malignancies {Johnson 2009, Leonard 2001, Olejniczak 2006, Rodriguez 1994, Uckun 1988} as well as all normal B lymphocytes in peripheral blood and spleen, but not by granulocytes, monocytes, platelets, erythrocytes, and T lymphocytes {Uckun 1988}. Briefly, the

anti-CD19 CAR comprises the following domains: an anti-human CD19 single-chain variable region fragment derived from the murine monoclonal antibody FMC63; the partial extracellular domain and complete transmembrane and intracellular signaling domains of human CD28, a lymphocyte costimulatory receptor that plays an important role in optimizing T-cell survival and function; and the cytoplasmic portion, including the signaling domain, of human CD3ζ, a component of the T-cell receptor complex {Nicholson 1997}. Following CAR engagement with $CD19^+$ target cells, the CD3ζ domain activates a downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector function.

Approval was based on ZUMA-1, a single-arm multicenter trial of 101 adult patients with aggressive B-cell NHL. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation. Patients received a single infusion of axicabtagene ciloleucel following completion of conditioning chemotherapy. Efficacy was established on the basis of an objective response rate (ORR) of 72% with a CR rate of 51%, as determined by an independent review committee (IRC) per {Cheson 2007, YESCARTA 2019}. In addition, the median duration of response (DOR) by IRC assessment per {Cheson 2007} was 9.2 months. The DOR was longer in patients with a best overall response of CR, as compared to a best overall response of partial remission {YESCARTA 2019}.

The most common Grade 3 or higher adverse reactions (incidence of 10% or greater) include febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Serious adverse reactions occurred in 52% of patients and the most common serious adverse reactions (> 2%) included encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. Fatal cases of CRS and neurologic toxicity occurred. The FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy {YESCARTA 2019}.

The dose of axicabtagene ciloleucel is a single intravenous (IV) infusion with a target of 2×10^6 CAR-positive viable T cells per kg body weight (maximum 2×10^8 CAR-positive viable T cells per kg body weight), preceded by fludarabine and cyclophosphamide conditioning chemotherapy. Axicabtagene ciloleucel is not indicated for the treatment of patients with primary CNS lymphoma. Additional details regarding the mechanism of action and clinical results of axicabtagene ciloleucel can be found in the Investigator's Brochure (IB).

2.4. Prior Anti-CD19 CAR T-cell Study Designs and Results

Refer to the current axicabtagene ciloleucel IB for the most current anti-CD19 CAR T-cell nonclinical and clinical information.

3. STUDY DESIGN AND RATIONALE

3.1. General Study Design

Study KTE-C19-112 (ZUMA-12) is a Phase 2 multicenter, open-label study evaluating the efficacy and safety of axicabtagene ciloleucel as first-line therapy in adult subjects with high-risk large B-cell lymphoma, including either HGBL with *MYC* and *BCL2* and/or *BCL6* translocations (double-/triple-hit lymphomas) or large B-cell lymphomas with high-intermediate-/high-risk IPI scores (≥ 3). Approximately 40 subjects will be enrolled upon a positive interim PET per the Lugano Classification {Cheson 2014} (Deauville 5-point scale [5PS] PET score of 4 or 5) after 2 cycles (PET2+) of standard-of-care chemoimmunotherapy.

Subjects will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- CCI [redacted]
- Conditioning chemotherapy period
- Investigational product treatment period
- Post-treatment assessment period
- Long-term follow-up (LTFU) period

At the end of ZUMA-12, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate LTFU study, KT-US-982-5968.

An independent Data Safety Monitoring Board (DSMB) will be chartered to meet and review the serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) on a semi-annual basis after the first subject has been treated with axicabtagene ciloleucel up through the primary analysis. Kite Pharma, Inc. (hereafter referred to as Kite or Kite Pharma), or delegate, will submit SAEs and SUSARs to the DSMB on a regular basis throughout the study up through the primary analysis. The DSMB will also meet to review safety data after 15 subjects have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 3 months after axicabtagene ciloleucel infusion. The DSMB will make trial conduct recommendations on an ongoing basis based on an analysis of risk versus benefit. The DSMB may request additional safety data for review or recommend modifications to the study conduct if safety concerns are identified. Refer to Section 9.10 for further details. For study requirements assigned to each study period, refer to the schedule of assessments (SOA) (Table 3) and Section 7 for details.

A study schema is described in Figure 1.

3.2. Study Design Rationale

ZUMA-12 is an open-label, single-arm study evaluating the efficacy and safety of axicabtagene ciloleucel as first-line therapy in adult subjects with high-risk large B-cell lymphoma (ie, double-/triple-hit lymphomas or large B-cell lymphoma with IPI scores ≥ 3).

CCI

[redacted]

Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and bi-specific T-cell engagers have demonstrated the potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. CAR-engineered T cells may address these issues and are an approach for cancer therapy.

Axicabtagene ciloleucel is an engineered autologous T-cell immunotherapy in which a patient's own T cells are collected and subsequently genetically altered to recognize CD19. CD19 is expressed on the cell surface of B-cell malignancies and normal B cells. In the pivotal ZUMA-1 Phase 1/2 trial, the safety and efficacy of axicabtagene ciloleucel were evaluated in patients with refractory DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma. In ZUMA-1, the ORR was 72% with a CR rate of 51%, as determined by an IRC per IWG 2007 criteria {Cheson 2007} and met the primary endpoint {YESCARTA 2019}. CCI

[redacted]

Axicabtagene ciloleucel may also have improved efficacy and tolerability in patients with less chemo-refractory disease or in patients with lower disease burden. CCI

[redacted]

Patients with double-/triple-hit lymphoma or high-intermediate-/high-risk IPI (IPI score ≥ 3) have a high unmet medical need. Therefore, axicabtagene ciloleucel will be assessed as first-line treatment in these high-risk large B-cell lymphoma patients who are also PET positive after 2 cycles (PET2+) of standard-of-care chemoimmunotherapy.

3.2.1. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in preclinical models, which demonstrate that the depth and duration of lymphodepletion correlates with antitumor activity of the adoptively transferred tumor-specific $CD8^+$ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. The cyclophosphamide and fludarabine combination is a potent conditioning chemotherapy regimen. Cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) are both given for 3 consecutive days. This combination has been studied in subjects with B-cell malignancies and was tolerated by this population {Kochenderfer 2017, O'Brien 2001}. The low-dose conditioning chemotherapy regimens used in these studies could not directly induce durable remissions. Low-dose cyclophosphamide and fludarabine alone increases interleukin (IL)-15, IL-7 and monocyte chemoattractant protein (MCP)-1 serum levels, which increased IL-15 serum levels is associated with efficacy of anti-CD19 CAR T cells {Kochenderfer 2017}. This low-dose cyclophosphamide and fludarabine conditioning chemotherapy was also used in the pivotal ZUMA-1 {Locke 2017, Neelapu 2017}

3.2.2. Rationale for Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on the aggregate safety and efficacy data compiled from ZUMA-1 as outlined in the IB. Based on the favorable benefit/risk ratio seen in ZUMA-1 and FDA approval for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, axicabtagene ciloleucel will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg but subjects may be dosed at a minimum of 1 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing $\geq$ 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2 x 10^8 anti-CD19 CAR T cells will be administered.

A positive risk benefit ratio is further supported by the expectation that subjects in this study will have a lower disease burden at the time of axicabtagene ciloleucel administration as they are receiving the dose earlier in their disease course compared to subjects in ZUMA-1 {Locke 2018}. In ZUMA-1, the observed response rates were consistent when comparing subsets with high versus lower tumor burden based on medians (ZUMA-1 clinical study report [CSR]; Section 11.1.1.3).

3.3. Participating Sites

Approximately 10 centers located in North America and the European Union will participate in this study and other regions may be considered. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.4. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that approximately 40 subjects will be enrolled and treated into this study.

3.5. Replacement of Subjects

Subjects may continue to be enrolled until the specified number of subjects are dosed with axicabtagene ciloleucel. Subjects who have not received axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (see Section 10.6).

3.6. Study Duration

3.6.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will be up to approximately 15 years. The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and timing of transition to the separate Kite LTFU study, KT-US-982-5968 (discussed in Section 7.13).

Following at least 36 months of assessments in the ZUMA-12 protocol, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in the separate LTFU study, KT-US-982-5968.

For a subject who completes participation in this study and also completes the LTFU period in the separate LTFU study, the entire duration of a subject's participation in both studies will be up to approximately 15 years after the initial infusion of axicabtagene ciloleucel. The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects and need to understand and mitigate the potential risks of delayed onset adverse events (AEs) that could be the potential consequence of this emerging technology.

3.6.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes at least 36 months of assessments, is lost to follow-up, withdraws consent, or dies. Upon activation of the LTFU study, KT-US-982-5968 at the subject's study site, the subject will be offered the opportunity to complete LTFU assessments under the KT-US-982-5968 protocol.

4. SUBJECT IDENTIFICATION ASSIGNMENT

Each subject who enters the screening period, which starts when the subject signs the informed consent form (ICF), will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. The subject identification number will never be changed even if the subject is rescreened.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

101) Large B-cell lymphoma with one or more of the following **features**:

a) HGBL with *MYC* and *BCL2* and/or *BCL6* translocations (double-hit or triple-hit) as determined by investigator by fluorescent in situ hybridization

OR

b) Other histologically confirmed large B-cell lymphoma defined by WHO 2016 {Swerdlow 2016} with an IPI score of ≥ 3 at initial diagnosis or anytime between initial diagnosis and enrollment, including the following lymphoma types:

i) DLBCL-NOS, including GCB type and ABC type

ii) Intravascular large B-cell lymphoma

iii) T-cell/histiocyte-rich large B-cell lymphoma

iv) DLBCL associated with chronic inflammation

v) Epstein-Barr virus + DLBCL-NOS

vi) HGBL-NOS

102) Subjects must have a positive interim PET per the Lugano Classification {Cheson 2014}(Deauville PET score of 4 or 5) after 2 cycles (PET2+) of chemoimmunotherapy as follows:

a) 2 cycles of an anti-CD20 monoclonal antibody (unless investigator determines that tumor is CD20 negative) and anthracycline-containing regimen (eg, DA-EPOCH-R), with or without intrathecal chemotherapy, at the discretion of the investigator per local standard of care for double-hit or triple-hit lymphoma

OR

b) 2 cycles of an anti-CD20 monoclonal antibody (unless investigator determines that tumor is CD20 negative) and anthracycline-containing regimen (eg, R-CHOP) at the discretion of the investigator per local standard of care for large B-cell lymphoma with IPI score of ≥ 3

103) At least 2 weeks must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis

104) No evidence, suspicion, and/or history of CNS involvement of lymphoma

105) Toxicities due to prior therapy must be stable and recovered to Grade 1 or less (except for clinically nonsignificant toxicities such as alopecia)

106) Age 18 or older

107) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

108) 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 and aspartate aminotransferase ≤ 2.5 upper limit of normal (ULN)

f) Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome

g) Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion (except trace or physiological) as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram findings

h) No clinically significant pleural effusion

i) Baseline oxygen saturation > 92% on room air

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

5.2. Exclusion Criteria

201) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease free for at least 3 years

202) History of Richter's transformation of chronic lymphocytic leukemia or PMBCL

203) History of autologous or allogeneic SCT

204) Prior CD19-targeted therapy

205) Prior CAR therapy or other genetically modified T-cell therapy

206) History of severe, immediate hypersensitivity reaction attributed to aminoglycosides

207) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management; simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the sponsor's medical monitor

208) History of human immunodeficiency virus (HIV) infection or acute or chronic active hepatitis B or C infection; subjects with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America guidelines or applicable country guidelines

209) 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, are permitted

210) Subjects with detectable cerebrospinal fluid malignant cells, brain metastases, or active CNS lymphoma

211) History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

212) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

213) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrollment

214) Requirement for urgent therapy due to tumor mass effects (eg, blood vessel compression, bowel obstruction, or transmural gastric involvement)

215) Primary immunodeficiency

216) History of autoimmune disease (eg, Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years

217) History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrollment

218) Any medical condition likely to interfere with assessment of safety or efficacy of study treatment

219) History of severe immediate hypersensitivity reaction to any of the agents used in this study

220) Live vaccine ≤ 6 weeks prior to planned start of conditioning regimen

221) Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential

222) Subjects of either sex who are not willing to practice birth control from the time of consent through 6 months after the completion of conditioning chemotherapy or axicabtagene ciloleucel infusion, whichever is longer

223) In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation

6. PROTOCOL TREATMENT

6.1. Study Treatment

6.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting peripheral blood mononuclear cells (PBMCs) that are used to manufacture axicabtagene ciloleucel.

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the Investigational Product Manual (IPM).

At least 2 weeks must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis.

CCI [redacted]

6.1.3. Conditioning Chemotherapy

Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of axicabtagene ciloleucel.

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted.

Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

6.1.3.1. Fludarabine

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Refer to the most recent version of the package insert for specific details surrounding the administration of fludarabine.

6.1.3.2. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard-derivative that acts as an alkylating agent following conversion to active metabolites in the liver and has potent immunosuppressive activity. The serum half-life after IV administration ranges from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Refer to the most recent version of the package insert for specific details surrounding the administration of cyclophosphamide.

6.1.3.3. Mesna

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient in mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$.

Mesna should be administered per institutional guidelines. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.1.4. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is the investigational product for this study.

CCI

There have been no instances of accidental overdose of subjects in this program to date. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of axicabtagene ciloleucel CCI research staff should report the problem per the instructions in the IPM.

Refer to the current version of the IB for more details regarding axicabtagene ciloleucel.

6.1.5. Concomitant Therapy

Concomitant therapy refers to treatment that subjects receive during the conduct of the study.

During the course of the study, investigators may prescribe any concomitant therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.1.6.

All concomitant therapies, including medications, intubation, dialysis, oxygen, and blood products, will be recorded.

For subjects who receive axicabtagene ciloleucel treatment:

- Concomitant therapies will be recorded from the date of the informed consent until 3 months after completing treatment with axicabtagene ciloleucel.

- After this 3-month follow-up period, targeted concomitant therapies will be recorded for either 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are enrolled, but not dosed with axicabtagene ciloleucel, concomitant therapies will be recorded from the date of the informed consent until 30 days after the last study-specific procedure has occurred (eg, leukapheresis, conditioning chemotherapy) or until the initiation of new antilymphoma therapy, whichever occurs first.

For subjects who are not enrolled (eg, screen failure), only concomitant therapies related to any SAE[s] will be recorded.

Specific concomitant therapy collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.1.6. Excluded Medications

Excluded medications refer to treatment that is not to be administered, unless otherwise specified, during the conduct of the study.

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to axicabtagene ciloleucel administration.

Systemic corticosteroids may not be administered as premedication to subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo noncontrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration unless used to manage axicabtagene ciloleucel-related toxicities. Other medications that might interfere with the evaluation of axicabtagene ciloleucel, such as nonsteroidal anti-inflammatory agents, should also be avoided for the same period unless medically necessary.

Therapeutic doses of systemic anticoagulants, such as unfractionated heparin and low-molecular weight heparin, should be avoided when possible anytime subjects are at risk of bleeding due to thrombocytopenia.

Treatments for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high-dose corticosteroids (other than those defined/allowed in this protocol) and other investigational agents, are prohibited, except as needed for treatment of disease progression after axicabtagene ciloleucel.

If permissibility of a specific medication/treatment is in question, contact the sponsor's medical monitor.

6.1.7. Subsequent Therapy

Subsequent therapy refers to treatment administered after axicabtagene ciloleucel that is necessary to treat a subject's disease.

Subsequent therapy administered after axicabtagene ciloleucel that is necessary to treat a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, will be recorded for subjects until one of the following happens: the subject transitions to the LTFU study KT-US-982-5968, is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled, but do not receive axicabtagene ciloleucel infusion, any additional anti-lymphoma therapy will also be collected until the subject completes their participation in the current study, is considered lost to follow-up, withdraws consent, or dies, whichever occurs first.

6.1.8. Toxicity Management

To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, cytopenias, and hypogammaglobulinemia. Refer to Section 6 of the current IB for details regarding these events and management guidance.

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important to always refer to the most current version of the axicabtagene ciloleucel IB for guidance regarding managing axicabtagene ciloleucel-related toxicities. Additional information and management recommendations can also be found in the IB regarding important potential risks associated with axicabtagene ciloleucel, as well as possible complications associated with malignancy and cancer treatment.

Refer to the SOA (Table 3) for the timing of evaluations for CRS-related symptoms.

7. STUDY PROCEDURES

Research staff should refer to the SOA (Table 3) for an outline of the procedures required.

The visit schedule is calculated from axicabtagene ciloleucel infusion on Day 0.

The visit schedule for disease assessments is also calculated from axicabtagene ciloleucel infusion on Day 0, including CT scans, PET scans, bone marrow biopsy, physical exams needed to assess disease, and collection of subsequent antilymphoma therapy.

An overview of study assessments/procedures is outlined below. Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Informed Consent

Before a subject participates in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequately explaining the study design, anticipated benefits, and potential risks. Subjects should sign the most current institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF before any nonstandard-of-care study-specific activity or procedure is performed.

The consent process and the subject's agreement or refusal to participate in the study must be documented in the subject's medical records. If the subject agrees to participate, the ICF must be signed and dated by both the subject and the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements, and a copy of the ICF will be provided to the subject.

All subjects who are enrolled into the study should be reconsented with any updated version of the IRB/IEC-approved ICF if the new version is relevant to their participation.

7.2. Screening

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected in the screening log should include limited information, such as the date of screening, date the subject was enrolled, or the reason for why the subject failed screening.

The screening period begins on the date the subject signs the IRB/IEC-approved ICF and continues through confirmation of eligibility into the study. Informed consent must be obtained before completion of any nonstandard-of-care study-specific procedures. Procedures that are part of standard of care are not considered study-specific and, therefore, may be performed prior to obtaining consent and used to confirm eligibility provided they occur within the time allowance outlined below and in the SOA.

After written informed consent has been obtained, Kite will assign a unique subject ID number to the subject.

See Section 7.2.1 for the study procedures for subjects who rescreen into the study. Only subjects who meet the eligibility criteria listed in Section 5 will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure within the subject's screening log, and the reasons for failing screening should also be recorded.

Refer to the SOA for a listing of study procedures to be completed during the screening period.

7.2.1. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period will be permitted to rescreen 1 time. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the original informed consent, it is only necessary to perform the procedure(s)/assessment(s) that did not originally meet the eligibility criteria; all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs after more than 28 days, or leukapheresis is delayed more than 28 days from the signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

7.3. Demographic Data

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity, and country of enrollment to study a possible association between these variables and subject safety and treatment effectiveness.

7.4. Medical and Treatment History

Relevant medical history prior to the start of AE reporting will be collected. Relevant medical history is defined as data on the subject's current medical condition that would be typically shared in a referral letter. In addition to the medical history, all history related to the subject's disease, treatment, and response to treatment will be collected and must date back to the original diagnosis. All findings will be recorded on the CRFs.

For subjects who are being referred from another clinic or institution to the participating research center, copies from the subject's chart should be obtained.

7.5. Conditioning Chemotherapy and Axicabtagene Ciloleucel Infusion

Administration of CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high-grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion. Signs, symptoms, or abnormal laboratory results attributed to the malignancy tumor fever and elevated C-reactive protein (CRP) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and axicabtagene ciloleucel infusion should be initiated only once it is reasonably assured that cell infusion can safely proceed.

Refer to Section 7.5.3 for requirements for workup of potential infectious and/or inflammatory states.

7.5.1. Requirements for Initiating Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the workup listed in Section 7.5.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- White blood cell (WBC) count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segs/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam including head, eyes, ears, nose, and throat (HEENT), and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- The treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with the infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (bacterial, viral serologies, polymerase chain reaction (PCR), stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with conditioning chemotherapy.

7.5.2. Requirements for Initiating Axicabtagene Ciloleucel Infusion

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the workup listed in Section 7.5.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of axicabtagene ciloleucel infusion
- CRP > 100 mg/L anytime between enrollment to start of axicabtagene ciloleucel infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of axicabtagene ciloleucel infusion WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segs/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam including HEENT, and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel (prophylactic use of antimicrobials is allowed).
- The treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with the infectious disease service (if applicable).
- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (bacterial, viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

Once the above criteria are met, then the subject can proceed with administration of axicabtagene ciloleucel.

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, protocol-specified conditioning chemotherapy must be repeated.

7.5.3. Requirements to Work-up Potential Infectious and/or Inflammatory States

In the absence of an identified source of infection (eg, line infection, pneumonia on chest x-ray), the minimum workup to be performed prior to administration of conditioning chemotherapy and/or axicabtagene ciloleucel consists of:

- Call Kite medical monitor
- Infectious disease service consult
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then noncontrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x 2 bottles each) and urinalysis and urine culture. Deep/induced sputum culture if clinically indicated
  - All indwelling lines, such as central venous catheters, should be examined for any signs of infection and additional cultures should be drawn from the line.
  - Nasopharyngeal-throat swab or equivalent assay for viral infection, such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (galactomannan, Fungitell®)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus)
- If a CNS process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy or axicabtagene ciloleucel infusion, the above workup must not suggest the presence of an active infection and all requirements for conditioning chemotherapy and axicabtagene ciloleucel infusion must be satisfied.

If the above workup was triggered due to CRP > 100 mg/L, testing for CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

7.5.4. Conditioning Chemotherapy Administration (Day –5 Through Day –3 Prior to Axicabtagene Ciloleucel Infusion)

Subjects will receive a conditioning chemotherapy regimen consisting of cyclophosphamide and fludarabine. The first dose of conditioning chemotherapy will be designated as Day –5. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 and through Day –3, with 2 rest days (Day –2 and Day –1) before receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting.

The 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions:

- IV hydration with a balanced crystalloid according to institutional guidelines prior to administration of cyclophosphamide on the day of infusion
- Cyclophosphamide 500 mg/m^2 IV over approximately 60 minutes or per institutional guidelines
- Fludarabine 30 mg/m^2 IV over approximately 30 minutes or per institutional guidelines
- Additional IV hydration with a balanced crystalloid according to institutional guidelines to be administered upon completion of the cyclophosphamide infusion
- Mesna to be administered per institutional guidelines

Subjects should be instructed to drink plenty of liquids during chemotherapy and throughout the 24-hour period following chemotherapy (approximately 2 L/24 hours). In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

Refer to the SOA Table 3 for a listing of study procedures to be completed during the axicabtagene ciloleucel conditioning chemotherapy period.

7.6. Physical Exam, Vital Signs, and Performance Status

Physical exams will be performed during screening and at times noted in the SOA. All physical exam changes noted in subsequent exams when compared to the baseline exam will be reported as AEs.

Vital signs, including blood pressure (BP), heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at screening and at times outlined in the SOA. In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after study treatment (see Section 6) and as clinically indicated.

Performance status as measured by the ECOG scale will be performed to quantify the subject's general well-being and ability to perform activities of daily life.

7.7. Cardiac Function

Each subject's cardiac function, as measured by left ventricular ejection fraction, will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion will also be confirmed, per study eligibility criteria. Both the left ventricular ejection fraction and pericardial effusion will be assessed prior to study entrance by an ECHO. An ECHO that was performed after the subject's last chemoimmunotherapy treatment may also be used to confirm eligibility, provided that it occurred ≤ 28 days prior to signing the consent.

To establish a baseline, a 12-lead electrocardiogram will also be performed during the screening period.

7.8. Neurological Examination

A neurological examination will be performed, and any of the following abnormalities will be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings (eg, speech, cognition, and emotion).

A neurological examination should be done prior to axicabtagene ciloleucel infusion on treatment Day 0, then on Day 1, Day 3, Day 5, and Day 7 during the observation period, which must last a minimum of 7 days.

For new onset of neurologic symptoms suspected to be related to axicabtagene ciloleucel treatment, refer to Section 6.1.8. Subjects will be specifically asked about changes in neurological status since the previous neurological examination, as noted in the SOA (see Table 3).

7.9. Disease Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the Lugano Classification {Cheson 2014} (see Appendix 1). Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

7.9.1. Imaging

7.9.1.1. Pre-treatment Disease Assessment

A fluorodeoxyglucose (FDG)-PET from skull base to mid-thighs and a diagnostic quality contrast-enhanced (unless contraindicated) CT from skull base through lesser trochanters (PET-CT), along with the appropriate imaging of all other sites of disease must be performed within 28 days prior to enrollment/leukapheresis.

If a PET-CT cannot be performed as standard of care following 2 cycles of chemoimmunotherapy, a subject may have the PET-CT performed on study after informed consent is obtained.

If the PET-CT performed following 2 cycles of chemoimmunotherapy is > 28 days from enrollment/leukapheresis [redacted], the PET-CT must be repeated to confirm subject remains PET2+.

7.9.1.2. Post-treatment Response Assessment

Post-treatment PET-CT response assessments will begin at Day 28 and continue at time points outlined in the SOA (Table 3). If there was evidence of baseline bone marrow involvement and no PET-CT is available or if there are unexplained cytopenias or suspicion of bone marrow involvement, then a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. To confirm a CR, the bone marrow aspirate and biopsy must show no evidence of disease by morphology, or, if indeterminate by morphology, must be negative by immunohistochemistry.

PET-CTs will continue through Month 24 or until disease progression, whichever comes first. If the subject's disease has not progressed by Month 24, disease assessments can then be performed at standard-of-care intervals. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if this requires an unscheduled visit. If the subject has started subsequent antilymphoma therapy, then imaging assessments will no longer be required per protocol. PET-CT can be performed at any time disease progression is suspected. FDG-PET assessment takes precedence over CT assessment for time points when both are available. If only CT is available for a particular time point, then the CT assessment should include a comparison with and may be affected by the PET-CT assessment at the prior time point. Please refer to the imaging manual for further details.

Bone marrow aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis as indicated. Refer to the IB for additional information.

7.9.1.3. Response Evaluation to Retreatment

For the purpose of determining response to retreatment with axicabtagene ciloleucel, the last scan prior to retreatment will be considered the baseline.

7.9.2. Determination of Bone Marrow Involvement

A subject's bone marrow involvement should be confirmed by PET-CT or bone marrow biopsy and aspirate prior to enrollment. Confirmation of marrow involvement from determination at initial diagnosis or between diagnosis and screening is acceptable.

7.10. Cell Collection and Axicabtagene Ciloleucel Study Treatment Schedule and Administration

7.10.1. Leukapheresis

Subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of leukapheresis.

If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and results are outside the eligibility criteria listed in Section 5, contact the sponsor's medical monitor prior to proceeding with leukapheresis.

Before leukapheresis commences, the following criteria must be met:

- No evidence or suspicion of an infection
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis

The leukapheresis visit should occur within approximately 5 days of eligibility confirmation. After a subject commences leukapheresis, the subject will be considered enrolled into the study.

If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed more than 5 days after eligibility confirmation, baseline complete blood count (CBC) with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the medical monitor prior to proceeding with leukapheresis.

After the above criteria are met, mononuclear cells will be obtained by leukapheresis (12 to 15 L) with a goal to target approximately 5 to 10 x 10^9 mononuclear cells. The leukapheresed cells are then packaged for expedited shipment to the manufacturing facility as described in the IPM.

Refer to the SOA Table 3 for a listing of study procedures to be completed on the leukapheresis collection day and as outlined in the SOA.

CCI [redacted]

[redacted]

7.10.3. Axicabtagene Ciloleucel Treatment Period

7.10.3.1. Axicabtagene Ciloleucel Premedication Dosing

The following pre-axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion:

- Acetaminophen 500 to 1000 mg taken orally or equivalent
- Diphenhydramine 12.5 to 25 mg administered either orally or via IV or equivalent

7.10.3.2. Axicabtagene Ciloleucel Administration Day 0

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility, followed by daily monitoring at a healthcare facility for ≥ 7 days to monitor for signs and symptoms of CRS and neurologic events. Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic events in the hospital setting, if deemed appropriate by the investigator. Post-infusion monitoring of subjects must be for a minimum of 7 days unless otherwise required by country regulatory agencies (refer to Appendix 3).

If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities resolve to Grade 1 or lower, or return to baseline. Subjects may be discharged with noncritical and clinically stable or improving toxicities (eg, renal insufficiency) even if higher than Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing neurologic events higher than Grade 1, or if deemed necessary by the investigator.

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects should be advised to refrain from driving and engaging in hazardous occupations or activities, such as or operating heavy or potentially dangerous machinery, for at least 8 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

Refer to the SOA for a listing of study procedures to be completed during the axicabtagene ciloleucel treatment period.

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the IPM. Vital signs should be measured during and after axicabtagene ciloleucel treatment (see Section 7.6).

Research sites should follow institutional guidelines for the infusion of cell products.

7.10.3.3. Axicabtagene Ciloleucel Retreatment

Subjects who achieve a partial response (PR) or CR and subsequently experience disease progression may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel. If subject is eligible, retreatment must occur within 24 months after the initial axicabtagene ciloleucel infusion.

The following criteria must be met prior to being considered for a repeat course of therapy:

- Subject had a PR or CR at any time after axicabtagene ciloleucel therapy and then subsequently progressed with CD19 tumor expression confirmed centrally by biopsy after disease progression and prior to retreatment
- Subject continues to meet the original study eligibility criteria with the exception of prior axicabtagene ciloleucel use in this study; screening assessments and procedures should be repeated if clinically indicated (eg, ECHO)
- Subject has not received subsequent therapy (see Section 6.1.7) for the treatment of lymphoma
- Subject did not experience a life-threatening toxicity related to axicabtagene ciloleucel during the original course of treatment
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to Grade 1 or lower, or returned to baseline prior to retreatment

Sites are required to collect a biopsy confirming disease progression and CD19 expression and to submit the biopsied tissue to the central laboratory before initiating retreatment.

The decision to retreat should be made in consultation with the sponsor's medical monitor. In addition, before performing any study-related procedures or treatment, it is necessary to 1) discuss the risks and benefits of retreatment with the subject, and 2) confirm with the subject how the second dose will be manufactured. The second dose could be manufactured at the same time that the first axicabtagene ciloleucel dose is made with existing cryopreserved PBMCs. Alternatively, the subject may need to undergo a second leukapheresis and should be informed of this possibility. These conversations should also be recorded in the subject's source document.

A maximum of 1 retreatment course may occur per subject. Subjects who are retreated will follow the same treatment schedule and procedural requirements per the initial treatment.

Allowance for retreatment is based on clinical experience in ZUMA-1, where a total of 10 subjects were retreated with axicabtagene ciloleucel (1 subject in Phase 1 and 9 subjects in Phase 2), and in ZUMA-7, where 9 subjects received retreatment with axicabtagene ciloleucel and were included in the retreatment analysis set.

Overall, in ZUMA-1, six of 10 retreated subjects had a PR or CR to the retreatment. The subject retreated in Phase 1 achieved a PR at Month 1 after retreatment. Among the 9 subjects retreated

in Phase 2, five subjects responded (2 CR and 3 PR) at Month 1. Analysis of duration of retreatment response (DORR) among the retreated subjects in Phase 2 showed a median DORR of 3.5 months.

In ZUMA-7, nine subjects were retreated with axicabtagene ciloleucel. After retreatment, 5 subjects had a response per central assessment, with all 5 subjects achieving a CR. Using the investigator assessment of response, 6 subjects had a response and 4 subjects had a CR.

After a subject is deemed eligible for retreatment and the means by which the second dose of axicabtagene ciloleucel has been confirmed (which will include determining whether a second leukapheresis is required), the subject will follow the study procedure requirements of the current IRB-approved protocol.

Re-treated subjects will be eligible for rollover to the LTFU study after completion of at least 36 months of assessments from the *initial* IP treatment.

7.11. Laboratory

7.11.1. Local Laboratory Analysis

Assessments listed in Table 2 will be performed at the local laboratory at the time points indicated in the SOA.

Table 2. Clinical Laboratory Parameters

Serum Chemistries	Hematology	Other
Albumin Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bicarbonate total Bilirubin total BUN or urea[a] Calcium total Chloride Creatinine Glucose Lactate dehydrogenase Magnesium total Potassium Sodium Uric acid[b]	CBC with differential[c]	C-reactive protein Ferritin Pregnancy test Viral testing[d]

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; EU, European Union.
a If BUN test cannot be analyzed by the local laboratory, urea should be analyzed.
b Per institutional guidelines.

c At the following pharmacokinetic time points, CBC with differential will be analyzed centrally: prior to leukapheresis, Day 7, Weeks 2 and 4, and Months 3, 6, 9, 12, and 24.
d For EU sites only, serologic tests (eg, human immunodeficiency virus, hepatitis B, hepatitis C, syphilis) may be carried out per institution guidelines and EU regulations

7.11.2. Central Laboratory Analyses

Assessment of CBC with differential will be submitted for central analysis at the following pharmacokinetic (PK) time points: prior to leukapheresis, Day 7, Weeks 2 and 4, and Months 3, 6, 9, 12, and 24.

Clinical biospecimens (eg, tumor, marrow, blood, cerebral spinal fluid [CSF], or other tissues) will be sent from clinical study centers to the central laboratory for sample processing, accessioning, and distribution to specialty laboratories.

- Biospecimens are obtained at the times indicated in the SOA and instructions regarding sample submission to central laboratories are provided in the Central Laboratory Manual.
- Biospecimens to be collected by study sites:
  - Archival tumor tissue (biopsy or slides) or fresh tumor sample if archive tissue is not available
  - CCI [redacted]
  - Bone marrow biopsy and aspirate, at baseline and/or post-treatment as needed, for confirmation of diagnosis and genetic analyses related specifically to large B-cell lymphoma
  - Blood for pharmacokinetics (levels of anti-CD19 CAR T cells), replication-competent retrovirus (RCR), and minimal residual disease (MRD) testing
  - Serum for pharmacodynamics (levels of serum cytokines)
  - CSF, if applicable, for pharmacokinetics and pharmacodynamics

CCI [redacted]

Multiple specialty laboratories may be employed for specific analyses. Refer to the Central Laboratory Manual for instructions regarding submitting such samples to the appropriate laboratory.

7.11.2.1. Central Confirmation of Diagnosis

Local diagnosis of large B-cell lymphoma for determination of study eligibility will be made by the investigator at each site. Diagnosis will be confirmed retrospectively by a centralized specialty laboratory (see Central Laboratory Manual) using tumor tissue in the form of an archival formalin-fixed paraffin-embedded block, unstained pre-cut slides, or fresh tumor tissue from an on-study baseline (prior to conditioning chemotherapy) biopsy, along with a pathology report.

This confirmation of diagnosis will include the following:

- Assessment of expression of other indication specific markers by immunohistochemistry or fluorescence in situ hybridization as needed for central confirmation of disease histology
- Morphological evaluation by hematoxylin and eosin staining
- Anatomical location of the biopsy
- Central review of local pathology report

If the central laboratory pathologist's diagnosis is discordant with local laboratory diagnosis, an additional pathologist will review the case for adjudication. If the interpretation remains discordant with the local laboratory diagnosis, the sponsor will be consulted to determine if the correct tissue block or slides was received. If the correct sample was received, the original slides used for local diagnosis will be requested for central review. If results are still discordant, the central laboratory's pathologist and the sponsor's medical monitor will review the documentation and images. The central diagnosis will be used in cases where adjudication fails to reach a concordant result with the local diagnosis. Additional details will be specified in the charter for the central specialty laboratory.

7.11.2.2. CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

Complete details concerning these analyses will be provided in separate documents CCI [redacted]

7.11.2.3. Pharmacokinetics and Pharmacodynamics

CCI

[redacted]

7.11.2.4. Product Characteristics

Samples of leukapheresis material or final product will be retained and tested by the sponsor or specialty laboratory for the purpose of understanding the mechanism of action and safety profile of axicabtagene ciloleucel.

7.11.2.5. Replication-competent Retrovirus Testing

Axicabtagene ciloleucel comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. Additional information is provided in the IB. The timing of blood draws for determination of the presence of RCR is specified in the SOA or may be done as clinically indicated.

RCR testing will occur at leukapheresis and at Months 3, 6, and 12. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up 15 years or as clinically indicated.

7.12. Post-treatment Assessment Period

After completing study treatment, all subjects will return to the clinic for post-treatment follow-up visits.

If a subject does not respond to treatment at any time during the post-treatment assessment period, then the subject will continue to undergo the post-treatment follow-up procedures per the SOA, and then be followed for survival and disease outcomes in the LTFU portion of the study starting with the Month 6 visit (Table 4).

Refer to the SOA (Table 3) for a listing of study procedures and disease assessments to be completed during the post-treatment follow-up period.

7.13. Long-term Follow-up Period

All enrolled subjects will be followed in the LTFU for safety analysis and survival and disease status for up to 15 years, if applicable. Subjects will begin the LTFU period beginning at the Month 6 visit. After completion of at least 36 months of assessments in the current protocol, subjects will transition to the LTFU study, KT-US-982-5968, after providing signed informed consent. Subjects who did not respond to treatment may receive off-protocol therapy but will continue to be followed for disease assessments (if progression was not documented), subsequent antilymphoma therapy, and survival.

Subjects may also be contacted by telephone to confirm survival status and subsequent antilymphoma therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or email to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, then the subject will be considered lost to follow-up, and no additional contact will be required.

Refer to the SOA (Table 4) for a listing of study procedures and disease assessments to be completed during the LTFU period.

Subjects who are enrolled but did not receive the investigational product will be followed only until the end of this study and will undergo the following assessments at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per protocol

All subjects who received an infusion of axicabtagene ciloleucel will transition to the LTFU study KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to axicabtagene ciloleucel as defined in Protocol KT-US-982-5968 and presence of RCR for up to 15 years from the time of axicabtagene ciloleucel infusion (also refer to Section 7.14).

In the LTFU study, KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

7.14. Summary of Scheduled Assessments

The SOA and the LTFU assessments are provided in Table 3 and Table 4, respectively.

Table 3. Schedule of Assessments

Procedure	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy					Axicabtagene Ciloleucel Administration		Post-treatment Follow-up (each visit calculated from Day 0)			
Visit	**Within 28 days of enrollment**	**Within approx. 5 days of eligibility confirmation**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D0**	**D1 to 7[a]**	**Week 2 (± 3 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Medical history	X												
Physical examination[b]	X		X	X	X			X		X	X	X	X
Neurological examination[c]	X							X	QOD		X		X
Weight (plus height at screening)	X	X											
Vital signs (BP, HR,RR, O_2 saturation, temperature)	X[d]	X	X	X	X			X	X	X	X	X	X
ECOG performance status	X												
Electrocardiogram	X										X		
ECHO[e]	X												
PET-CT disease assessment[f]	X[d]										X		X
Archival /Fresh tumor sample[g]	X								D7-14				
Pregnancy test (serum or urine)	X	X[h]	X[h]										X
Blood draw for chemistry panel	X	X	X	X				X	X	X	X	X	X
Blood draw for CBC with differential[i]	X	X	X	X				X	X	X	X	X	X
Blood draw for serology (EU sites)[j]	X	X											
Blood draw for LDH	X												
Blood draw for MRD											X		X

Procedure	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy					Axicabtagene Ciloleucel Administration		Post-treatment Follow-up (each visit calculated from Day 0)			
Visit	Within 28 days of enrollment	Within approx. 5 days of eligibility confirmation	D-5	D-4	D-3	D-2	D-1	D0	D1 to 7[a]	Week 2 (± 3 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Lumbar puncture[k]	X												
CCI	CCI												
Blood draw for CRP/ferritin		X						X	X				
CCI	CCI												
Blood draw for RCR analysis[n]		X											X
Blood draw for cytokines[o]		X						X	D1, D3, D7	X	X		
CCI	CCI												
Leukapheresis		X											
Fludarabine/Cyclophosphamide			X	X	X								
Axicabtagene ciloleucel intravenous infusion								X					
Adverse events/Concomitant therapy[p]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP, blood pressure; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CRP, C-reactive protein; CRS, cytokine release syndrome; D, day; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, heart rate; LDH, lactate dehydrogenase; MRD, minimal residual disease; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography; PK, pharmacokinetics; QOD, every other day; RCR, replication-competent retrovirus; RR, respiratory rate.

a Axicabtagene ciloleucel administration period, refer to Appendix 3 for requirements by country regulatory agencies.

b Subjects with new onset symptoms related to CRS should undergo physical examination at least daily until symptoms resolve to baseline. Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam, will have a brain MRI and lumbar puncture for examination of cerebral spinal fluid. A physical exam is required prior to the start of conditioning chemotherapy and prior to axicabtagene ciloleucel infusion.

c Neurologic assessment: A neurological assessment should be done prior to axicabtagene ciloleucel infusion on treatment Day 0, on treatment Day 1, Day 3, Day 5, and Day 7 during the minimum 7-day observation period. For new onset of neurologic symptoms or if neurologic symptoms persist, neurologic examination will be performed at least daily until symptoms resolve to baseline.

d In addition to the time points outlined in the SOA, it is recommended that vital signs are monitored during and after study treatment (see Section 6) and as clinically indicated.

e ECHO will be performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

f PET-CT will be performed within 28 days prior to enrollment. If bone marrow involvement was not evaluated within 28 days of enrollment, a PET-CT or a bone marrow biopsy will be performed to establish a baseline. PET-CT shall be performed at any time disease progression is suspected. If there is evidence of baseline bone marrow involvement, or if there are unexplained cytopenias, or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm complete response. CCI [redacted].

g Either formalin-fixed paraffin-embedded tumor block or 30 unstained slides will be required. If an archived tumor sample is not available, a fresh tumor sample is required prior to start of chemotherapy to continue on study. CCI [redacted] Archived and fresh tumor samples (if applicable) will be submitted to a central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Slides that have been previously stained with antibodies or other reagents are not acceptable. Screen failed subjects' archived samples should not be submitted. CCI [redacted]

h Pregnancy test (serum or urine): EU only: test to be completed within 7 days prior to both leukapheresis and conditioning chemotherapy for females of childbearing potential.

i At the following time points, CBC with differential will be analyzed centrally: prior to leukapheresis, Day 7, Weeks 2 and 4, and Month 3.

j For EU sites, serologic test (eg, HIV, hepatitis B, hepatitis C, syphilis) will be carried out per institutional guidelines and EU regulations. This may be done within 30 days prior to leukapheresis or on the day of leukapheresis.

k Subjects with symptoms of CNS malignancy (eg, new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade 2 or higher neurologic symptoms after axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid when feasible. Measuring the opening pressure should be done, if possible, with recording of the results in the subject site chart.

l CCI [redacted]

n Blood draws for RCR will be collected prior to leukapheresis and at Months 3, 6, and 12 then collect yearly for up to 15 years. Yearly samples will only be collected/analyzed if positive at Month 3, 6, or 12. Blood and serum samples may also be used for further RCR evaluation as clinically indicated.

o Blood draws for cytokines will be collected prior to leukapheresis, on Day 0 prior to administration of axicabtagene ciloleucel, on Days 1, 3, 7, and Weeks 2 and 4. If a subject who was admitted to the hospital within the 7-day observation period is discharged and then subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related adverse events, blood samples for cytokines will be collected on the day of hospital re-admission and then weekly through and including the day of discharge. Blood samples for cytokines will also be collected at the time of disease progression prior to starting any subsequent antilymphoma therapy. If the subject experiences a Grade 3 or higher axicabtagene ciloleucel-related toxicity, such as a Grade 3 CRS or neurologic event, 1 additional blood draw for cytokines will be taken at the time of the Grade 3 or higher axicabtagene ciloleucel-related toxicity and upon resolution of the event.

p Adverse events will be recorded from the date of enrollment until 3 months after completing treatment with axicabtagene ciloleucel. Concomitant therapies will be recorded from the date of informed consent until 3 months after completing treatment with axicabtagene ciloleucel.

Table 4. Long-term Follow-up Assessments

Procedure	Long-term Follow-up Period Each visit calculated from Day 0 (all visits have ± 28 day window)												
Visit frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36 [a]**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Thereafter**
Physical examination (with neurological examination)[b]	X	X	X	X	X	X							
PET-CT disease assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for CBC with differential[d]	X	X	X	X	X	X							
CCI	CCI												
CCI	CCI												
Blood draw for RCR analysis[f]	X		X			X		X		X		X	X
CCI	CCI												

Procedure	Long-term Follow-up Period Each visit calculated from Day 0 (all visits have ± 28 day window)												
Visit frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36 [a]**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Thereafter**
Targeted AEs/SAEs[g]	X	X	X	X	X	X							
Targeted concomitant medications[h]	X	X	X	X	X	X							
Subsequent therapy for NHL[i]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; CT, computed tomography; NHL, non-Hodgkin lymphoma; PET-CT, positron emission tomography–computed tomography; MRD, minimal residual disease; RCR, replication-competent retrovirus; SAE, serious adverse event.

a After completion of at least 36 months of assessments in ZUMA-12, subjects who received an infusion of axicabtagene ciloleucel will transition to the LTFU study KT-US-982-5968 after providing signed informed consent, to complete the remainder of the 15-year LTFU period.

b Physical exams will continue through Month 24.

c PET-CT/disease assessments will continue through Month 24 or until disease progression, whichever comes first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per standard of care.

d Blood draw for CBC with differentials will continue through Month 24 or until disease progression, whichever comes first.

[redacted]

f Blood draws for RCR analysis will continue through Month 12. Yearly samples will only be collected/analyzed if positive at Month 3, 6, or 12. Blood and serum samples may also be used for further RCR evaluation as clinically indicated.

g After 3 months, only targeted AEs/SAEs will be reported. Targeted AEs/SAEs are defined as infections; neurological, hematological, and autoimmune disorders; and secondary malignancies that occur up to 15 years after axicabtagene ciloleucel infusion or until disease progression (whichever occurs first).

h Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first).

i Subsequent therapy refers to therapy administered after axicabtagene ciloleucel infusion for a subject's disease, such as non-study-specified chemotherapy, immunotherapy, target agents, as well as stem cell transplant and radiation therapy, which must be collected until the subject completes the LTFU period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.

8. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study-required treatment and/or other protocol-required procedures at any time during the study while continuing to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from the investigational product, study treatment, or other protocol-required therapies and must also discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy, undergo procedures, and continue participating in study follow-up. Subject data collected up until withdrawal of consent will be retained and included in the analysis of the study. Publicly available data (death records) can be included after withdrawal of consent if local regulations permit. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may be asked to also retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

8.1. Reasons for Removal from Treatment

Reasons for removal from protocol-required investigational products or procedures include any of the following:

- AEs
- Subject request
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

8.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision
- Lost to follow-up
- Death

9. SAFETY REPORTING

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record. The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or BP has increased in a subject with pre-existing hypertension).

A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs. Hospitalization for study-treatment infusions or precautionary measures per institutional policy are not considered AEs.

The term "disease progression," as assessed by measurement of malignant lesions on radiographs or other methods, should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported under the primary tumor type (eg, B-cell lymphoma).

When an AE or SAE is due to the disease under investigation, it is necessary to report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. If a subject requests to withdraw from protocol-required therapies or the study because of an AE, then the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject that occur after enrollment (ie, commencement of leukapheresis) through 3 months after treatment with axicabtagene ciloleucel infusion.

After 3 months, targeted AEs (eg, infections, neurological, hematological, and autoimmune disorders, and secondary malignancies) will be monitored and reported for 15 years after treatment with axicabtagene ciloleucel or until disease progression, whichever occurs first.

For subjects who are enrolled, but do not receive axicabtagene ciloleucel, the AE reporting period ends 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy).

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to axicabtagene ciloleucel, conditioning chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) axicabtagene ciloleucel, 2) conditioning chemotherapy, 3) any protocol-required study procedure or treatment, 4) disease progression, 5) concurrent disease, 6) concomitant medication, or 7) other. The relationship is indicated by a Yes or No response and entered into the CRF. A Yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

The investigator is expected to follow reported AEs until stabilization or resolution. If a subject begins a new antilymphoma therapy, the AE reporting period for non-SAEs ends at the time the new treatment is started.

9.2.1. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

An abnormal laboratory test result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Is associated with clinical symptoms
- Results in a medical intervention (eg, potassium supplementation for hypokalemia or iron replacement therapy for anemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

9.3. Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

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

An AE would meet the criterion of "requires hospitalization" if the event necessitated an admission to a healthcare facility (eg, overnight stay).

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the existing planned hospitalization.

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded on the electronic CRF (eCRF).

9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through 3 months after the axicabtagene ciloleucel infusion or until the initiation of another antilymphoma therapy, whichever occurs first. After 3 months, only targeted SAEs will be reported. Targeted SAEs are defined as and include infections; neurological, hematological, and autoimmune disorders; and secondary malignancies that occur up to 15 years after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first.

SAEs, which the investigator assesses as related to axicabtagene ciloleucel, should be reported regardless of the time period.

For subjects who screen fail or are enrolled but do not receive axicabtagene ciloleucel, the reporting period for SAEs ends 30 days after the last study-specific procedure (eg, screening procedure, leukapheresis, conditioning chemotherapy).

All SAEs must be submitted to Kite via the electronic SAE system within 24 hours of the investigator's knowledge of the event. If the electronic SAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and emailed to the SAE Reporting mailbox: safety_fc@gilead.com.

Following completion of ZUMA-12, any relevant information on ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the **paper SAE Report Form** and sent via e-mail to the SAE Reporting mailbox: safety_fc@gilead.com.

Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded on the CRF as AEs or SAEs and indicated as being due to disease progression. If the malignancy has a fatal outcome before the end of the SAE reporting period, then the event leading to the death must be recorded as an SAE with the outcome being fatal.

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment.

Any death occurring after the first dose of chemotherapy, for the purpose of pre-conditioning, and within 3 months of axicabtagene ciloleucel infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment.

9.5. Reporting Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying lymphoma should be recorded as SAEs with the preferred term "B-cell lymphoma" and must be reported immediately to the sponsor. Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Refer to the CRF completion guidelines for detailed instructions.

9.6. Diagnosis Versus Signs and Symptoms

For AEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and the signs and symptoms will be captured on the AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

9.7. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Women of childbearing potential should be monitored according to local and country-specific regulations. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after conditioning chemotherapy dosing or the administration of axicabtagene ciloleucel, whichever is longer. Male subjects are recommended to not father a child for at least 6 months after the conditioning chemotherapy dosing or the administration of axicabtagene ciloleucel, whichever is longer. Refer to Appendix 4 for a complete list of highly effective contraception methods.

If a pregnancy occurs in either a female subject enrolled into the study or a female partner of a male subject within 6 months of completing conditioning chemotherapy or the administration of axicabtagene ciloleucel, whichever is longer, the pregnancy must be reported to the sponsor. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

The pregnancy should be reported to the sponsor within 24 hours of the investigator's knowledge of the pregnancy event by using the pregnancy report form and emailing it to: safety_fc@gilead.com.

The pregnancy outcome should be reported to the sponsor using the pregnancy outcome report form and emailing it to: safety_fc@gilead.com.

Lactation cases occurring in female patients taking protocol-required therapies (PRT) and up to 6 months after PRT should be reported to safety_fc@gilead.com within 24 hours of awareness using the lactation reporting form.

9.8. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE as described in Section 9.4.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative care or hospice care
- Planned hospitalization required by the protocol (eg, for monitoring of the subject or to perform an efficacy measurement for the study)
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying cancer

9.9. Abnormal Vital Sign Values

Not all vital sign abnormalities qualify as an AE. A vital sign result must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding if an isolated vital sign abnormality should be classified as an AE. However, if a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high BP), only the diagnosis (ie, hypertension) should be recorded on the CRF.

9.10. Data Safety Monitoring Board

An independent DSMB will be chartered to meet and review the SAEs and SUSARs on a semi-annual basis after the first subject has been treated with axicabtagene ciloleucel up through the primary analysis. Kite Pharma, or delegate, will submit SAEs and SUSARs to the DSMB on a regular basis throughout the study up through the primary analysis. The DSMB will also meet to review safety data after 15 subjects have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 3 months after axicabtagene ciloleucel infusion. The DSMB will make trial conduct recommendations on an ongoing basis based on an analysis of risk vs benefit. The DSMB may request additional safety data for review or recommend modifications to the study conduct if safety concerns are identified. The DSMB may meet more often as needed.

The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review. At the time of expedited reporting of SUSARs to the FDA, Kite Pharma (or designee) will concurrently submit these reports to the DSMB chair.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis will be tested. This study is designed to estimate the CR rate in subjects with high-risk large B-cell lymphoma. The CR rate targeted in this study is 60%.

10.2. Study Endpoints

10.2.1. Primary Endpoint

CR rate is defined as the incidence of a CR per the Lugano Classification {Cheson 2014} as determined by study investigators. All evaluable subjects who do not meet the criteria for a CR by the analysis data cutoff date will be considered non-responders.

The final analysis will be performed on subjects in this study after at least 36 months of follow-up. Subjects will be transitioned to the KT-US-982-5968 study for the remainder of the 15-year LTFU period. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10.2.2. Secondary Endpoints

ORR is defined as the incidence of either a CR or a PR per the Lugano Classification {Cheson 2014} as determined by the study investigators. All evaluable subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

DOR is defined only for subjects who experience an objective response after axicabtagene ciloleucel infusion and is the time from the first objective response to disease progression per the Lugano Classification {Cheson 2014} or death from any cause. Subjects not meeting the criteria for disease progression or death from any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive any subsequent new antilymphoma therapy, including SCT in the absence of documented disease progression or death, will be censored at the last evaluable disease assessment prior to the subsequent new antilymphoma therapy.

EFS is defined as the time from the axicabtagene ciloleucel infusion date to the earliest date of disease progression per the Lugano Classification {Cheson 2014}, commencement of subsequent new antilymphoma therapy including SCT, or death from any cause. Subjects alive, in response, and with no new antilymphoma therapy including SCT will be censored at the last evaluable disease assessment.

PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the Lugano Classification {Cheson 2014} or death from any cause. Subjects not meeting the criteria for disease progression or death from any cause by the analysis data cutoff date will be censored at the last evaluable disease assessment. Subjects who receive any subsequent new antilymphoma therapy including SCT in the absence of documented disease progression or death will be censored at the last evaluable disease assessment prior to the subsequent new antilymphoma therapy.

OS is defined as the time from axicabtagene ciloleucel infusion to the date of death from any cause. Subjects who are alive will be censored at their last date known to be alive or the data cutoff date, whichever is earlier. Subjects who die after the data cutoff date will be censored at the data cutoff date.

Relapse with CNS disease is defined as the time from the axicabtagene ciloleucel infusion date to the earliest date of CNS involvement with lymphoma, as determined by typical symptoms, CSF evaluation, and/or diagnostic imaging.

Incidence of AEs (including Grade 3 or higher, serious, fatal, and AEs of interest) and clinically significant changes in safety laboratory values. Additional secondary endpoints include PK and pharmacodynamic endpoints, such as the evaluation of anti-CD19 CAR T-cell levels in the blood and cytokine levels in the serum in relationship with clinical outcome.

10.2.3. CCI

CCI

10.2.4. Covariates and Subgroups

The following covariates at screening/baseline may be used in efficacy and safety analyses:

- Age (< 65, ≥ 65 years)
- Gender
- Race
- Ethnicity
- ECOG status
- IPI score
- Diagnosis category (double-hit lymphomas versus triple-hit lymphomas versus non-double-/triple-hit with IPI score ≥ 3)
- Levels of cytokines
- Levels of CAR T cells
- CR achieved on the study

Additional associative analyses of covariates with subject outcomes will be specified in the statistical analysis plan.

10.3. Sample Size Considerations

In the GELA randomized Phase 2 study evaluating the efficacy of R-ACVBP or R-CHOP-14 induction, using IWF 2007 criteria in young patients with high-risk DLBCL, the primary objective of achieving a higher than 50% CR rate after 4 cycles of induction regimen was not met in both randomization groups (47% in R-ACVBP and 39% in R-CHOP-14) {Casasnovas 2017}. Accordingly, it is postulated that a CR rate of 60% would represent a clinically meaningful improvement over standard chemoimmunotherapy in a high-risk large B-cell lymphoma patient population. Although there is no formal hypothesis testing, the sample size has been determined in part with descriptive analysis described below.

The trial uses a single-arm design to estimate the CR rate in subjects with high-risk large B-cell lymphoma treated with axicabtagene ciloleucel. A CR rate of 60% with axicabtagene ciloleucel treatment is targeted. With a total sample size of 40 subjects, an observed CR rate of 60% will yield an 80% CI for the response rate with a maximum half-width of less than or equal to 11%, corresponding to a lower limit of at least 48.6%. This target CR rate, and the lower limit of the 80% CI for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with high-risk large B-cell lymphoma and would likely offer an improvement over existing therapies in patients with high-risk large B-cell lymphoma.

Table 5 provides the estimated CR rate and the lower and upper limits of 80%/95% CI based on the Clopper-Pearson method for a range of possible CR rates for a sample of 40 subjects.

Table 5. Lower and Upper Limits of 80%/95% CIs for CR Rates from 60% to 100% for a Sample of 40 Subjects

Number (%) of CRs	24 (60)	28 (70)	32 (80)	36 (90)	40 (100)
Lower and upper limits of 80% CI (%, %)	48.6, 70.6	58.8, 79.5	69.6, 88.0	81.0, 95.6	94.4, 100
Lower and upper limits of 95% CI (%, %)	43.3, 75.1	53.5, 83.4	64.4, 90.9	76.3, 97.2	91.2, 100

Abbreviations: CI, confidence interval; CR, complete response.

10.4. Access to Individual Subject Treatment Assignments

This is a single-arm, open-label study, and subjects and investigators will be aware of treatment received. Data-handling procedures for the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical plan, DSMB charter, and trial integrity document.

10.5. Interim Analysis and Early Stopping Guidelines

The DSMB will meet and review SAEs and SUSARs on a semi-annual basis after the first subject has been dosed. The DSMB may request additional safety data.

One planned interim analysis will be performed. Interim Analysis 1 will be conducted after 15 subjects have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 3 months after axicabtagene ciloleucel infusion. This analysis will be for efficacy and safety and will be descriptive.

10.6. Analysis Subsets

In this study, subjects are to be dosed at a target of 2×10^6 (1.0×10^6 to 2.4×10^6) anti-CD19 CAR T cells/kg. A minimum dose of 1×10^6 anti-CD19 CAR T cells/kg may be administered. For subjects weighing ≥ 100 kg, a maximum flat dose of 2×10^8 anti-CD19 CAR T cells will be administered. Subjects are considered to have received the target dose if they receive at least 1×10^6 anti-CD19 CAR T cells/kg.

The safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel. This analysis set will be used for all safety data analyses.

The full analysis set will consist of all enrolled/leukapheresed subjects and will be used for the summary of subject disposition and the listing of deaths.

The response evaluable analysis set will consist of the subjects who are enrolled and treated with axicabtagene ciloleucel at a dose of at least 1×10^6 anti-CD19 CAR T cells/kg and have a centrally confirmed disease type (double-/triple-hit lymphomas) or large B-cell lymphoma with an IPI score ≥ 3. This analysis set will be used for all efficacy data analyses including CR rate, ORR, endpoints based on response (DOR, EFS, and PFS), relapse with CNS, and OS.

10.7. Planned Method of Analysis

The primary analysis will occur after all treated subjects have an opportunity to be assessed for response 6 months after the Week 4 disease assessment. The CSR will be written based on the data collected and analyzed from this primary analysis. The final analysis will occur after all subjects complete at least 36 months of follow-up.

The primary analysis of CR rate will be based on the investigator's review of disease assessments in the response evaluable analysis set.

10.7.1. CR Rate

The subject incidence of CR will be calculated. The 2-sided 80%/90%/95% CIs will be provided about the CR rate, calculated with the Clopper-Pearson method.

10.7.2. ORR

The subject incidence of objective response will be calculated. The 2-sided 80%/90%/95% CIs will be provided about the ORR, calculated with the Clopper-Pearson method.

The incidence of subjects with CR, PR, stable disease, PD, not done, and not evaluable, as best overall response to treatment, and exact 2-sided 80%/90%/95% CIs about the incidence will be generated.

10.7.3. DOR

Kaplan-Meier plots, estimates, and 2-sided 80%/90%/95% CIs will be generated for DOR among the subjects who achieve an objective response. Kaplan-Meier estimates of the proportion of subjects alive and PFS at 3-month intervals will be provided. The number of subjects censored or having events and the reasons for censoring or type of events (PD or death) will be summarized.

A sensitivity analysis of DOR will be conducted in which disease assessments obtained after SCT (for subjects who undergo SCT while in an axicabtagene ciloleucel-induced response) will be used in the derivation of DOR.

DOR may be evaluated in subgroups defined by the covariates described in Section 10.2.4.

10.7.4. EFS

Kaplan-Meier plots, estimates, and 2-sided 80%/90%/95% CIs will be generated for EFS. Kaplan-Meier estimates of the proportion of subjects alive and event-free at 3-month intervals will be provided. The number of subjects censored or having events, and the reasons for censoring or type of events (PD, subsequent new antilymphoma therapy, or death) will be summarized.

EFS may be evaluated in subgroups defined by the covariates described in Section 10.2.4.

10.7.5. PFS

Kaplan-Meier plots, estimates, and 2-sided 80%/90%/95% CIs will be generated for PFS. Kaplan-Meier estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided. The number of subjects censored or having events, and the reasons for censoring or type of events (PD or death) will be summarized.

PFS may be evaluated in subgroups defined by the covariates described in Section 10.2.4.

10.7.6. OS

Kaplan-Meier plots, estimates, and 2-sided 80%/90%/95% CIs will be generated for OS. Estimates of the proportion of subjects alive at 3-month intervals will be provided through 2 years after the final subject has been enrolled and then annually through the completion of the study. The number of subjects censored or having events, and the reasons for censoring or type of events (death) will be summarized.

OS may be evaluated in subgroups defined by the covariates described in Section 10.2.4.

10.7.7. Relapse with CNS Disease

The number of subjects with CNS relapse and time to relapse with CNS disease among the subjects who experience CNS relapse will be summarized.

Relapse with CNS disease may be evaluated in subgroups defined by the covariates described in Section 10.2.4.

10.7.8. Safety

Subject incidence rates of AEs, including all, serious, fatal, CTCAE Grade 3 or higher, treatment-related AEs, and AEs of interest reported throughout the conduct of the study, will be tabulated by system organ class and preferred terms or preferred terms only, coded with the Medical Dictionary for Regulatory Activities. Changes in laboratory values and vital signs will be summarized with descriptive statistics.

The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through the LTFU and treatment-related SAEs will be provided.

The incidence, prevalence, duration, and reversibility of identified risks, RCR, and secondary malignancies will be summarized.

10.7.9. Pharmacokinetic Analysis

The levels of anti-CD19 CAR T cells measured in peripheral blood at Day 7 after axicabtagene ciloleucel infusion will be summarized with descriptive statistics.

10.7.10. Pharmacodynamics Analyses

The levels of cytokines in serum will be summarized with descriptive statistics.

10.7.11. CCI [redacted]

The analyses CCI [redacted] will be detailed CCI [redacted]

11. REGULATORY OBLIGATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable local laws and regulations

11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators will submit site-specific and study SAEs (provided to the site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

11.2. Subject Confidentiality

Subject confidentiality must be maintained within all material that is submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique ID number
- Year of birth/age at time of enrollment will be reported according with local laws and regulations

For the reporting of SAEs, subjects will be identified by their respective subject ID number, initials, and year of birth (as per their local reporting requirements for both initials and year of birth).

Per country-specific regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, contract research organization, IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes personal information.

11.3. Investigator Signatory Obligations

Each CSR will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite under the following criteria:

- Is a recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participated in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the investigator's agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma and the investigator reserve the right to terminate the investigator's participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC regarding either the trial completion or early termination and provide the contract research organization with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at its sole discretion, to determine whether to manufacture axicabtagene ciloleucel and provide it to sites and subjects after the completion of the study.

13. STUDY DOCUMENTATION AND ARCHIVING

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. The individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and patient charts; laboratory, pharmacy, and radiology records; subject diaries; microfiches; correspondence; and death registries. CRF entries may be considered as source data if the site of the original data collection is not available. However, the use of the CRFs as source documentation is not recommended as a routine practice.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and or audited at any time by the key sponsor contact, health authorities, and IRB/IECs. The filing system will include at a minimum:

- Subject content including ICFs and subject ID lists
- Protocols and protocol amendments, IB, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite and the investigator. If storage is no longer available to archive source documents, or if source documents must be moved to an alternative location, the research staff should notify the key sponsor contact prior to shipping the documents.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors, or regulatory inspectors are responsible for contacting, and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records must also assure that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence and accuracy and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records as identified in Section 13.

By signing the investigator's agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH/GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility(ies), review of subject- and study-related records, and compliance with protocol requirements as well as ICH/GCP and applicable regulatory policies.

All data will be collected in an electronic CRF system. All entries must be completed in English and concomitant therapies should be identified by tradenames. For further details surrounding the completion of CRFs, please refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-112 (ZUMA-12) will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states that authorship should be based on:

- Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; and
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data, or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite for review and approval. The study contract among the institution, principal investigator, and Kite or its delegate will outline the requirements for publication review.

16. COMPENSATION

Kite will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

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18. APPENDICES

Appendix 1. Lugano Classification {Cheson 2014}

Please refer to {Cheson 2014} for details of assessment.

Deauville 5-Point Scale (5PS) {Barrington 2014}

Score	Description
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Complete Remission:

Complete Metabolic Response for Positron Emission Tomography–Computed Tomography-Based Response

The designation of complete metabolic response requires all of the following:

- A 5PS (5-point scale) score of 1, 2 or 3, with or without a residual mass
  - In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may be greater than normal in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No new sites of disease should be observed
- No evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow

Complete Radiologic Response for Computed Tomography-Based Response

The designation of complete radiologic response requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter (LDi) of a lesion
- No extralymphatic sites of disease
- Absent nonmeasured lesion

- Organ enlargement regress to normal
- No new sites of disease should be observed
- Bone marrow normal by morphology; if indeterminate, immunohistochemistry negative

Partial Remission:

Partial Metabolic Response for Positron Emission Tomography–Computed Tomography-Based Response

The designation of partial metabolic response requires all of the following:

- A 5PS score of 4 or 5, with reduced uptake compared to baseline (screening), and residual mass(es) of any size

  Note:

  — At interim, these findings suggest responding disease

  — At end of treatment, these findings suggest residual disease
- No new sites of disease should be observed
- Residual uptake is higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake is compatible with reactive changes from chemotherapy allowed)

If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with magnetic resonance image or biopsy or an interval scan.

Partial Radiologic Response for Computed Tomography-Based Response

The designation of partial radiologic response requires all of the following:

- ≥ 50% decrease in sum of the product of the perpendicular diameters of up to 6 target measurable nodes and extranodal sites

  — When a lesion is too small to measure on a computed tomography scan, assign 5 mm x 5 mm as the default value

  — When no longer visible, 0 x 0 mm

  — For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
- Absent/normal, regressed, but no increase of nonmeasured lesions
- Spleen must have regressed by > 50% in length beyond normal
- No new sites of disease should be observed

Stable Disease:

No Metabolic Response for Positron Emission Tomography–Computed Tomography-Based Response

The designation of no metabolic response requires all of the following:

- A 5PS score of 4 or 5, with no significant change in FDG uptake compared to baseline (screening) at an interim time point or end of treatment
- No new sites of disease should be observed
- No change from baseline in bone marrow

Stable Radiologic Disease for Computed Tomography-Based Response

The designation of stable radiologic disease requires all of the following:

- < 50% decrease from baseline in the sum of the product of the perpendicular diameters of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
- No increase consistent with progression in nonmeasured lesion and organ enlargement
- No new sites of disease should be observed

Progressive Disease:

Progressive Metabolic Disease for Positron Emission Tomography–Computed Tomography-Based Response

The designation of progressive metabolic disease requires at least 1 of the following:

- A 5PS score 4 or 5 with an increase in intensity of uptake from baseline and/or
- New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered
- New or recurrent FDG-avid foci in bone marrow

Progressive Radiologic Disease for Computed Tomography-Based Response

The designation of progressive radiologic disease requires at least one of the following:

- An individual node/lesion must be abnormal with:
  - LDi > 1.5 cm and
  - Increase by ≥ 50% from cross product of LDi and perpendicular diameter nadir and
  - An increase in LDi or SDi, shortest axis perpendicular to the LDi, (SDi) from nadir
    - 0.5 cm for lesions ≤ 2 cm
    - 1.0 cm for lesions > 2 cm
  - In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, spleen must increase by at least 2 cm from baseline
  - New or recurrent splenomegaly
- New or clear progression of pre-existing nonmeasured lesions
- New lesion
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

Appendix 2. International Prognostic Index in Aggressive Lymphomas

The International Prognostic Index (IPI) score is calculated by adding the number of prognostic factors:

- Age > 60 years
- Performance status ≥ 2
- Lactate dehydrogenase > 1 x normal
- Extranodal sites > 1
- Stage III or IV

The IPI risk level is determined based on the IPI score:

Risk Level	IPI Score
Low (L)	0 or 1
Low-intermediate (LI)	2
High-intermediate (HI)	3
High (H)	4 or 5

Appendix 3. Country-Specific Regulatory Agency Requirements

France

The post-infusion monitoring of subjects, described in Section 7.10.3.2 of this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "Axicabtagene Ciloleucel Administration Period, D1 to 7." The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.6), blood draw for chemistry panel with C-reactive protein, blood draw for complete blood count with differential, and neurological examination (see Section 7.8). Any observed toxicity will be managed according to Section 6.1.8 of this protocol.

Appendix 4. Birth Control Methods Which May Be Considered as Highly Effective

For the purpose of this guidance, methods that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[2]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device[2]
- Intrauterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial subject and that the vasectomized partner has received medical assessment of the surgical success.
[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.