CLINICAL STUDY PROTOCOL

Protocol Title:	A PHASE 2 OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL CONCOMITANT WITH PROPHYLACTIC STEROIDS IN SUBJECTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA IN THE OUTPATIENT SETTING
Protocol Number	KT-US-482-0137
Study Nickname:	(ZUMA-24)
Indication:	Relapsed or refractory (r/r) large B-cell lymphoma (LBCL)
Kite Investigational Product:	axicabtagene ciloleucel
IND Number:	016278
EU CT Number:	Not applicable
Clinical Trials.gov Identifier:	NCT05459571
Sponsor Name and Address:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Contact Information:	The medical monitor name and contact information is provided on the Key Study Team Contact List
Protocol Version/Date:	Original: 18 February 2022
Amendment History:	Amendment 1.0: 13 September 2023 Amendment 2.0: 29 March 2024 Amendment 3.0: 05 February 2025

This study will be conducted under United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application regulations (21 Code of Federal Regulations Part 312).

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory and local requirements.

CONFIDENTIALITY STATEMENT

This document contains confidential information of Kite Pharma, Inc., a wholly owned subsidiary of Gilead Sciences Inc. This document must not be disclosed to anyone other than the study site research staff, collaborators, and members of the Institutional Review Board/Independent Ethics Committee, a scientific review board, or an equivalent. The information in this document cannot be used for any purpose other than the conduct of the clinical investigation without the prior written consent of Kite Pharma, Inc.

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PROTOCOL SYNOPSIS

Kite Pharma, Inc.
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Protocol Title: A PHASE 2 OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL CONCOMITTANT WITH PROPHYLACTIC STEROIDS IN SUBJECTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA IN THE OUTPATIENT SETTING

Protocol Number (Study Nickname): KT-US-482-0137 (ZUMA-24)

Indication: Relapsed or refractory (r/r) large B-cell lymphoma (LBCL)

Kite IND Number: 016278

EU CT Number: Not applicable

Clinical Trials.gov Identifier: NCT05459571

Kite Investigational Product: axicabtagene ciloleucel

Other Investigational Product /IND Number:

Not applicable.

Number of Study Sites Planned: Approximately 20

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• Evaluate the rate and severity of cytokine release syndrome (CRS) and neurologic events following outpatient administration of axicabtagene ciloleucel	Incidence rate and severity of CRS and neurologic events
Secondary Objectives	**Secondary Endpoints**
• Characterization of the expanded safety profile including, time to onset and duration of CRS/neurologic events, patterns of hospitalization, incidence and duration of infections/cytopenias • Change in the European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) over time. • Assessment of clinical efficacy • Assessment of pharmacokinetics and pharmacodynamics, including the levels of anti-CD19 chimeric antigen receptor (CAR) T-cells and serum pro- inflammatory, immuno-modulatory and effector molecules.	• Time to onset and duration of CRS and neurologic events following axicabtagene ciloleucel administration • Rates of hospitalization after axicabtagene ciloleucel infusion as measured by proportion of hospitalized subjects within 72 hours, 3 days after infusion date 7 days, 14 days, and 30 days. • Duration of initial hospitalization after axicabtagene ciloleucel infusion • Proportion of intensive care unit (ICU) admitted subjects • Duration of ICU admission during first hospitalization after axicabtagene ciloleucel infusion

	• Safety of axicabtagene ciloleucel as measured by the incidence of adverse events (AEs) and serious adverse events (SAEs) • Change of EQ5D-5L from Baseline to Month 6 • Efficacy of axicabtagene ciloleucel as measured by objective response rate (ORR), complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), event- free survival (EFS) (all per investigator assessment), and overall survival (OS) • Blood levels of key serum analytes (including cytokines, defined in Section 5.27) and axicabtagene ciloleucel CAR T-cells over time
Exploratory Objectives	**Exploratory Endpoints**
• Explore the pattern of worsening of CRS and neurologic events following axicabtagene ciloleucel administration (ie, time from initial event grade to higher grade) • Exploration of the utility of electronic wearable technology in outpatient monitoring and assessment of predictive modeling for outpatient selection for axicabtagene ciloleucel treatment	• Time from end of axicabtagene ciloleucel infusion to: — Initial CRS and progression to higher grade CRS — Initial neurologic events, and progression to higher grade neurologic events — Tocilizumab administration — Corticosteroid administration (aside from prophylactic dexamethasone per protocol) — Administration of vasopressors — Administration of supplemental oxygen for documented hypoxemia • Number of urgent care/emergency department visits and/or unscheduled outpatient visits with/without subsequent hospital admission • Cumulative use of corticosteroids and other concomitant medications of interest • Phenotypes and functional attributes of pre-infusion axicabtagene ciloleucel (product characterization) • Extended characterization of serum and plasma analytes and their association with clinical outcome

Study Design: Study KT-US-482-0137 is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with r/r LBCL in the outpatient setting.

Approximately 30 subjects will be enrolled and treated in this Phase 2 study.

Each subject will follow the same study treatment schedule and procedural requirements as outlined in the schedule of assessments (SOA; Table 7 and Table 8).

A study schema is provided in Figure 1.

The outpatient monitoring after axicabtagene ciloleucel infusion is required as described in Section 5.6.3. All subjects will be required to undergo outpatient monitoring visits daily at least for the first 7 days following axicabtagene ciloleucel infusion and less frequently thereafter according to the treating physician's discretion. In addition, each subject should undergo vital signs check (temperature, heart rate [HR], respiratory rate [RR], blood pressure [BP] and oxygen saturation [spO_2]) at a regular interval according to institutional guidelines throughout each day while away from treatment facility for at least the first 7 days. Any abnormalities should be reported to the treatment team. Subjects are to be evaluated by the treating team on an urgent basis as appropriate. All subjects are to stay in close proximity (2-hours travel distance) to the treating center for at least 4 weeks after infusion.

Guidelines for Hospitalization

CRS, any grade

Abnormal neurological event, any grade

Other criteria at the discretion of the covering physician.

For Grade 1 and 2 CRS (eg, fevers, hypotension responsive to fluids, hypoxia responsive to O_2 nasal canula) and Grade 1 neurological events, subjects may be admitted for outpatient observation at the discretion of the treating physician. If symptoms persist for longer than 8 hours and /or recur within 24 hours, the subject should be admitted to the inpatient setting for closer monitoring and evaluation.

Number of Subjects Anticipated to be Enrolled and Treated:

Approximately 30 subjects will be enrolled and treated in this study.

Target Population:

Male or female adults ≥ 18 years of age with r/r LBCL

Duration of Treatment and of Study Participation:

Subjects will receive 1 infusion of axicabtagene ciloleucel.

The duration of the study will be approximately 18 months. The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and timing of the transition to the separate Kite long-term follow-up (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 from the time of the initial infusion of axicabtagene ciloleucel.

Diagnosis and Main Eligibility Criteria:

Key Inclusion Criteria

1) Histologically confirmed LBCL, including the following types defined by World Health Organization (WHO) 2016 classification {Swerdlow 2016}, by local pathology laboratory assessment, are eligible as defined below:
   a) Diffuse large B-cell lymphoma (DLBCL) not otherwise specified
   b) High-grade B-cell lymphoma (HGBL) with or without MYC and BCL2 and/or BCL6 rearrangement
   c) DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV) + DLBCL
   d) Primary mediastinal (thymic) LBCL
   e) Primary cutaneous DLBCL, leg type
   f) Transformation of follicular lymphoma to DLBCL will also be included
2) Relapsed or refractory disease after 1 or more lines of therapy.
3) Subjects must have received adequate prior therapy including:
   a) Anti-CD20 monoclonal antibody AND
   b) An anthracycline-containing chemotherapy regimen
4) At least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.
5) Age 18 or older
6) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7) Subject agrees to outpatient treatment setting and to adhere to the prespecified clinical monitoring requirements outlined in the SOA

Key Exclusion Criteria:

1) History of autologous or allogeneic stem cell transplant
2) Prior CD19 targeted therapy
3) Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy
4) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor.

5) Subjects with detectable cerebrospinal fluid (CSF) malignant cells, brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma. DLBCL epidural involvement should be considered as positive CNS disease
6) 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

Investigational Product and Study Treatments, Dose, and Mode of Administration:

Subjects will receive lymphodepleting (conditioning) chemotherapy. The lymphodepleting chemotherapy regimen will consist of cyclophosphamide 500 mg/m^2/day IV and fludarabine 30 mg/m^2/day IV infused over 3 days (Days −5, −4, and −3) and before administration of axicabtagene ciloleucel.

Axicabtagene ciloleucel treatment will consist of a single infusion of CAR-transduced autologous T-cells administered intravenously on Day 0 at a target dose of 2 X 10^6 cells/kg intravenously. Prior to the axicabtagene ciloleucel infusion on Day 0, on Day 1, and on Day 2, subjects will receive prophylactic dexamethasone 10 mg IV/PO.

All subjects will receive axicabtagene ciloleucel infusion without being hospitalized. However, all subjects need to stay in close proximity (within-2 hours travel distance) to the clinic for immediate access to the treating team for urgent clinical evaluation and/or hospital admission. All subjects need to follow the SOA, especially in the first 2 weeks of axicabtagene ciloleucel infusion.

Study Procedures: As outlined in the SOA, subjects will undergo the following procedures: collection of informed consent, medical history; physical exam; neurological examination; ECOG performance status; disease staging, including a baseline positron emission tomography-diagnostic computed tomography (PET-diagnostic CT); brain magnetic resonance image (MRI) or contrast enhanced CT scan if contraindication to MRI; and blood draws for lactate dehydrogenase levels (LDH), complete blood count (CBC), serum chemistries, axicabtagene ciloleucel CAR and other biomarkers, including pharmacokinetics and pharmacodynamics; collection of archival and/or fresh tumor biopsy at screening and after axicabtagene ciloleucel infusion might also be performed (as per SOA). Subjects will also undergo baseline echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan and electrocardiogram (ECG) assessments and may also need bone marrow aspirate/biopsy and lumbar puncture if medically necessary. Women of childbearing potential will undergo a urine or serum pregnancy test.

Routinely throughout the conduct of the study, all subjects will be asked to report concomitant therapies, AEs, and subsequent lymphoma therapy.

Subjects will undergo leukapheresis for the collection of peripheral blood mononuclear cells necessary for axicabtagene ciloleucel manufacturing. Lymphodepleting (conditioning) chemotherapy will be followed by 2 rest days and then infusion of axicabtagene ciloleucel. Prior to axicabtagene ciloleucel infusion on Day 0, on Day 1, and on Day 2, subjects will receive prophylactic dexamethasone 10 mg daily. Subjects will undergo a daily outpatient monitoring

visit for at least 7 days after axicabtagene ciloleucel infusion to manage any AEs, and less frequently thereafter per the treating physician's discretion. Subjects and caregivers should remain in close proximity (within 2-hours travel distance) of the study site for at least 4 weeks after axi-cel infusion. Blood draws for the analysis of anti-CD19 CAR T-cell levels will be performed.

Additional blood draws for cytokines and replication-competent retrovirus (RCR) are performed as clinically indicated, as presented in the SOA.

Subjects will be followed for approximately 18 months in the current protocol after which subjects may roll over to LTFU study (KT-US-982-5968). If the study is terminated early, all subjects who were infused with axicabtagene ciloleucel will be transitioned to the LTFU study, KT-US-982-5968, at the time of study termination.

Safety Review Team: A safety review team (SRT) will review the available composite safety after the first 6 subjects have been dosed and have had the opportunity to be followed for at least 14 days to analyze risk versus benefit. Enrollment will be paused when the sixth subject is dosed and resumed after this safety evaluation as detailed in the SRT charter. Available pharmacokinetics/pharmacodynamics and efficacy outcomes will also be reviewed. If no unacceptable safety risk due to outpatient dosing is identified, the enrollment will be resumed, and the study will continue with continuous real-time monitoring of safety outcomes.

In order to evaluate the feasibility of the outpatient approach and to inform the Sponsor's decision on whether to continue the study, the SRT will also perform a review when approximately 20 enrolled and treated subjects have been followed for at least 14 days after axicabtagene ciloleucel infusion. Enrollment will be paused when the 20th subject is dosed and resumed after this safety evaluation as detailed in the SRT charter.

Safety and efficacy data will be under continuous monitoring.

Statistical Methods:

Hypothesis: No formal hypothesis will be tested. All analyses will be descriptive.

Sample Size Calculation: This study uses an open-label, single-arm design, with the planned sample size of up to 30 subjects.

Safety Review: The SRT will perform the overall benefit/risk assessment at the time points mentioned above. Safety endpoints (incidence and severity, time to onset and duration of CRS and neurologic events, admission rate and duration of hospitalization and ICU, time to first hospitalization, overall AE summaries including identified and potential risks, deaths, adverse events of special interest (AESIs), and other important safety endpoints) and available for pharmacokinetics/pharmacodynamics and efficacy endpoints (ORR, CR rate, DOR, EFS, PFS, and OS) will be provided.

The primary analysis will occur when all subjects (approximately 30) have been treated and have had the opportunity to be evaluated for 6-months after the infusion. The primary endpoints, incidence and severity of CRS by modified Lee 2014 and neurologic events by Common Terminology Criteria for Adverse Events (CTCAE) v5.0, will be based on the safety analysis set,

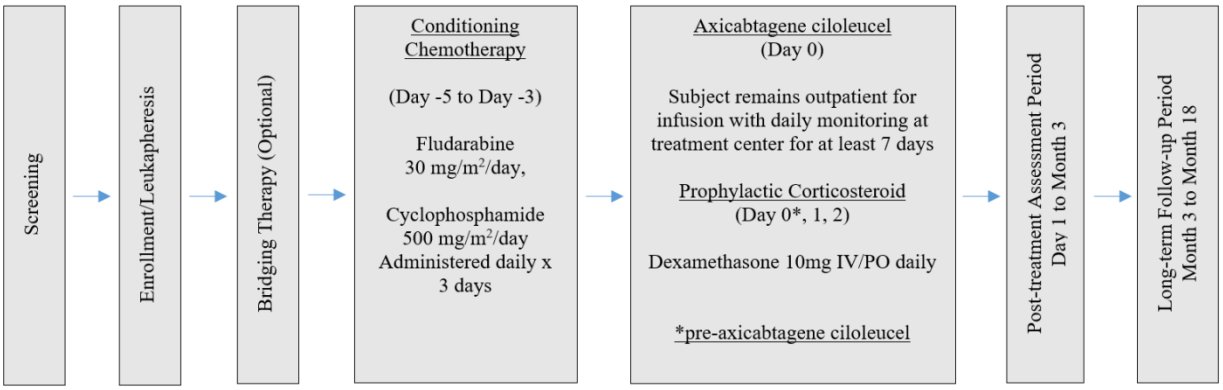
which includes all subjects treated with axicabtagene ciloleucel. Efficacy endpoints will be based on the efficacy evaluable set, which consists of all subjects enrolled and treated with axicabtagene ciloleucel at a target dose of 2 x10^6 anti-CD19 CAR-T cells/kg and who have documented disease at baseline and subsequent tumor assessment following axicabtagene ciloleucel infusion. Analyses of the safety and efficacy endpoints of this study will be entirely descriptive, with no formal statistical testing being performed.

At various timepoints throughout the study, ad hoc data analyses may be conducted to review the ongoing safety and efficacy outcomes.

The final analysis will occur when all enrolled subjects have withdrawn from the study, have been lost to follow up, have died, or have entered the LTFU study.

STUDY SCHEMA

Figure 1. Study and Treatment Schema



- Collection of peripheral blood mononuclear cells (PBMCs) from subjects will be performed through leukapheresis (enrollment)
- Conditioning chemotherapy regimen consists of administration of fludarabine 30mg/m^2 and cyclophosphamide 500mg/m^2 for 3 consecutive days (Day -5 through Day -3)
- Prophylactic corticosteroids consist of administration of dexamethasone 10mg by mouth orally or IV on Day 0 (prior to axicabtagene ciloleucel), Day 1, and Day 2
- Axicabtagene ciloleucel treatment consists of single infusion of chimeric antigen receptor (CAR)-transduced autologous T-cells administered intravenously on Day 0 (following dexamethasone 10mg) at the following target dose: 2 X 10^6 cells/kg
- Subject and caregiver are to remain in close proximity (2 hour driving distance) to treatment center for 4 weeks following axicabtagene ciloleucel infusion

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interests
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
AUC	area under the curve
CAR	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic leukemic lymphoma
CNS	central nervous system
CPF	cell processing facility
CR	complete response/remission
CRF	Case Report Form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CXCL-10	C-X-C motif chemokine ligand
ddPCR	droplet digital polymerase chain reaction
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
DORR	duration of retreatment response
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
EFS	event free survival
EMA	European Medicines Agency

EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Scale
eSAE	electronic serious adverse event
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GP	general practitioner
HR	Hazard ratio
HBsAg	hepatitis B
HCP	healthcare provider
HCV	hepatitis C
HEENT	head, eyes, ears, nose, and throat
HGBL	High-grade B-cell lymphoma
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IP	investigational product
IPM	Investigational Product Manual
IRB	Institutional Review Board
IV	intravenous(ly)
KM	Kaplan Meier
LDH	lactate dehydrogenase
LBCL	large B-Cell lymphoma
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MCP-1	monocyte chemotactic protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma

NT	neurologic toxicity
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PMBCL	primary mediastinal B-cell lymphoma
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PET-diagnostic CT	positron emission tomography-diagnostic computed tomography
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcome
QTc	corrected QT
RCL	replication-competent lentivirus
RCR	replication-competent retrovirus
r/r	relapsed/refractory
SAA	serum amyloid A
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
sPO2	oxygen saturation
SOA	schedule of assessments
SOCT	standard of care therapy
SRT	safety review team
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFL	transformed follicular lymphoma
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Disease Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes, or natural killer cells. In the United States (US). NHL is the most prevalent hematological malignancy, accounting for 4% of all new cancer cases and 3% of cancer-related deaths {National Cancer Institute (NIH) 2022}. For 2019, an estimated 74,000 new cases of NHL and approximately 20,000 deaths due to NHL in the US were expected to occur {National Cancer Institute (NIH) 2022}. In 2020, 122,979 new cases of NHL were reported in Europe and 49,684 deaths were attributable to NHL {World Health Organization (WHO) 2020}. Large B-cell lymphoma (LBCL, ie, diffuse LBCL [DLBCL], high grade B-cell lymphoma [HGBL], and primary mediastinal B-cell lymphoma [PMBCL]) is the most common and is an aggressive subtype of B-cell NHL, accounting for approximately 30% to 40% of cases {Chaganti 2016, Morton 2006, Sehn 2015}, with approximately 22,000 new diagnoses in the US each year {Elstrom 2010, Flowers 2010}. The addition of rituximab into combination therapies for LBCL has greatly improved patient outcomes. However, patients with chemotherapy- refractory DLBCL still have a poor prognosis {Flowers 2010}.

1.2. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy directed against the B-cell-specific cell surface marker CD19 has been indicated for the treatment of adult patients with relapsed or refractory (r/r) LBCL after 2 or more lines of systemic therapy. Approval of axicabtagene ciloleucel in the US, European Union (EU), and other regions was based on results from clinical study ZUMA-1 Cohort 1 and 2, which demonstrated improved efficacy relative to historical response rates with an objective response rate (ORR) of up to 83% and a complete response (CR) rate of up to 58% {Locke 2019}. At a subsequent analysis with a minimum follow-up of 24 months, 39% of subjects were in an ongoing response {Jacobson 2020}. Median overall survival (OS) was 25.8 months and 5-year OS rate was 43% (ASH 2021). Despite these improved clinical outcomes compared to historical treatment options, the safety profile of CAR-T cell therapy do warrant close monitoring and specific and timely management of, namely cytokine release syndrome (CRS) and neurologic events (NE). In ZUMA-1, Grade ≥ 3 CRS and neurologic toxicity (NT) occurred in ~10% and ~30% of patients, respectively. To this end, the majority of patients who receive axicabtagene ciloleucel in the commercial setting are dosed and monitored in an inpatient setting.

Most recently, ZUMA-7, a phase 3, randomized open-label multicenter study evaluating the efficacy of axicabtagene ciloleucel compared with standard of care therapy (SOCT) as a second line therapy in LBCL met its primary endpoint of event free survival (EFS) compared to SOCT arm (stratified hazard ratio [HR]: 0.378 [95% confidence interval [CI]: 0.308, 0.514]; stratified log-rank p <0.0001). A 6 months (ie, 4.15-fold) improvement in median EFS and an event-free rate at 2 years that was 2.5 times higher was observed in the axicabtagene ciloleucel arm compared with the SOCT arm (median EFS time: 8.3 months and 2.0 months, respectively; 2-year event-free rate: 40.5% versus 16.3%, respectively). These results may well change the

practice paradigm for LBCL in the second line setting. In terms of safety, 6% of patients developed Grade ≥3 CRS and 21% of subjects developed Grade ≥3 NE. Median time to CRS onset was 3 days. Median time to neurologic events onset was 7 days. There were no grade 5 events {Locke 2022}. Of note, ZUMA-7 did not utilize the safety management algorithm of ZUMA-1 Cohort 6.

Refer to the current Investigator's Brochure (IB) for additional information on axicabtagene ciloleucel.

1.3. Summary of Relevant Nonclinical and Clinical Studies With Axicabtagene Ciloleucel

1.3.1. Nonclinical Studies With Axicabtagene Ciloleucel

Nonclinical studies demonstrated that anti-CD19 CAR-T cells can recognize and eliminate CD19+ tumor cell lines, providing the initial proof-of-concept for use of axicabtagene ciloleucel in the treatment of patients with B-cell malignancies that express CD19.

Refer to the current IB for additional information on axicabtagene ciloleucel nonclinical studies.

1.3.2. Clinical Studies With Axicabtagene Ciloleucel

On 18 October 2017, the US Food and Drug Administration (FDA) approved axicabtagene ciloleucel for the treatment of adult patients with r/r large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, HGBL, and transformed follicular lymphoma (FL) {YESCARTA 2019}. On 23 August 2018, the European Medicines Agency (EMA) approved axicabtagene ciloleucel for the treatment of adult patients with r/r DLBCL and PMBCL after 2 or more lines of systemic therapy {YESCARTA 2021}. Both approvals were based on results of Study KTE-C19-101 (hereafter referred to as ZUMA-1), a single-arm, multicenter study of 108 adult subjects with r/r aggressive large B-cell NHL {Neelapu 2017}. Among 101 subjects in the Phase 2 pivotal cohorts who were assessable for efficacy, the ORR was 83%, and the CR rate was 58%. At a median follow-up of 27.1 months, 37% of subjects remained in ongoing response, median OS was not reached and 50.5% of subjects remained alive at 24 months. Of the 108 subjects who received axicabtagene ciloleucel in Phases 1 and 2, 52 (48%) had grade 3 or worse serious adverse events (SAEs). Grade 3 or worse cytokine release syndrome (CRS) occurred in 12 (11%) patients, and grade 3 or worse neurological events in 35 (32%) {Locke 2019}. With a median follow -up of 63.1 months, responses were ongoing in 31% of patients with median OS of 25.8mos. ZUMA-1 demonstrated sustained overall and disease specific survival with the estimated 5 year OS rate of 42.6% and disease specific survival estimated at 51.0%. No new safety signal was identified {Neelapu 2023}

Among all treated subjects in ZUMA-1, the most common Grade 3 or higher adverse reactions (incidence ≥ 10%) were febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections with pathogen unspecified, hypotension, hypoxia, and lung infections. Two fatal CRS events occurred {Locke 2019, YESCARTA 2021}. In the US, axicabtagebe ciloleucel was approved with a Risk Evaluation and Mitigation Strategy (REMS) requirement.

In 2022, Yescarta gained approval in the US, EU, and a number of other countries for the treatment of patients with r/r LBCL after 1 line of therapy based on the results of ZUMA-7, a pivotal phase 3 randomized controlled study of axicabtagene ciloleucel in the second line setting compared to standard of care therapy (SOCT). With a median follow-up of 2 years, ZUMA-7 met the primary endpoint of event-free survival (EFS; HR 0.398, $p < 0.0001$). Six percent of patients experienced Grade 3 or higher CRS with a median onset of 3 days, and 21% experienced neurological events Grade 3 or higher. No new safety concerns were identified in this second-line setting. {Locke 2022}. At a median follow-up of 47.2 months, the estimated 4 year overall survival was significantly longer in the axi-cel arm at 54.6% compared to that of the SOC arm at 46.0% (HR, 0.73; 95% CI, 0.54 to 0.98; P=0.03) {Westin 2023}

There has been an ongoing effort to understand factors associated with CRS and neurologic events associated with cellular therapies to mitigate these treatment-related toxicities. To this end, several safety management strategies were explored in the phase 2 portion of ZUMA-1 (Cohorts 3 to 6) to assess the impact of prophylactic tocilizumab (Cohort 3), earlier toxicity management with tocilizumab and corticosteroids (Cohort 4), tumor debulking (Cohort 5), and prophylactic steroid use in addition to earlier toxicity management with tocilizumab and corticosteroids (Cohort 6) on the rate and severity of CRS and NE. In particular, Cohort 6 (n=40), which employed prophylactic dexamethasone 10mg daily on Day 0, Day 1, and Day 2, in addition to early intervention of tocilizumab and corticosteroids for CRS and NE, showed an improved safety profile with an incidence of Grade 3 or higher CRS and NE of 0% and 13%, respectively. Furthermore, median time to CRS onset was also delayed to 5 days (versus 2 days for Cohort 1 and 2). Comparable efficacy was seen with an ORR of 95% and ongoing response of 53% after 12 months of follow-up. Comparable pharmacokinetic profiles for both peak and area under the curve (AUC) were also observed {Oluwole 2021}.

Refer to the current IB for additional information on other ongoing clinical studies being conducted with axicabtagene ciloleucel.

1.4. Study Rationale

In this study, we aim to show that, similar to ZUMA-1 Cohort 6, concomitant administration of prophylactic steroids, in addition to early intervention of tocilizumab and steroids for CRS/NE, will reduce the rate and severity of axicabtagene ciloleucel-related CRS and neurologic events and also delay the onset of CRS in relapsed/refractory LBCL after 1 or more lines of therapy. Further, delayed onset of CRS with prophylactic steroids, when combined with careful patient monitoring and timely escalation of care, will enable patients to be treated in the outpatient setting and only be hospitalized when clinically indicated.

1.5. Benefit/Risk Assessment for the Study

Efficacy results in studies of axicabtagene ciloleucel demonstrate that a single treatment with axicabtagene ciloleucel at a dose of 2×10^6 cells/kg following low-dose conditioning chemotherapy achieved a statistically significant increase in ORR relative to the prespecified control rate. Axicabtagene ciloleucel administered as a single infusion has also demonstrated unprecedented response rates, including CRs in more than 50% of these subjects, in a setting of high unmet medical need.

Axicabtagene ciloleucel continues to demonstrate a positive benefit-risk profile and offers a clear and robust treatment option for patients with r/r LBCL; including DLBCL NOS, PMBCL, and TFL; after 2 or more lines of systemic therapy. Outcomes with other available therapies are poor for patients who have r/r LBCL {Colosia 2014, Crump 2004, Feugier 2005, Van Den Neste 2016}. Collectively, patients with r/r LBCL have no curative options and a clear unmet medical need exists.

The risks of axicabtagene ciloleucel therapy are well described. Identified risks include CRS and neurologic events, which have an early onset, generally within 7 days after the therapy, and are mostly reversible. Severe and occasional life-threatening events, including CRS and neurologic events, have occurred. Strategies have been developed for these AEs to monitor for early detection and management of the risks, and the rates of severe CRS and neurologic events have been shown to have decreased over the course of studies of axicabtagene ciloleucel.

The overall benefit-risk profile continues to be positive: the benefits of axicabtagene ciloleucel outweigh the risks, including severe and occasionally life-threatening events. Axicabtagene ciloleucel is administered as a single dose following lymphodepleting (conditioning) chemotherapy, and the majority of adverse events (AEs) occur within 30 days of infusion. AEs, which can be severe or occasionally life threatening, are well defined, generally reversible and manageable, with no apparent long-term consequences other than B-cell aplasia. The rates of severe CRS and neurologic events decreased over the course of the ZUMA-1 study, whereas efficacy remained consistent.

Axicabtagene ciloleucel provides an important and effective treatment option for patients with r/r LBCL. As of the DCO of 17 October 2021, the benefit-risk profile for axicabtagene ciloleucel has not changed. Overall, the safety information received during the reporting period is consistent with previous knowledge of the safety profile of axicabtagene ciloleucel, and benefits that may be afforded by axicabtagene ciloleucel continue to outweigh the identified and potential risks. Lastly, this study will evaluate the risks and benefits and safety of out-patient treatment of axicabtagene ciloleucel for r/r LBCL at centers in the US according to their respective out-patient monitoring guidelines.

Refer to the current version of the IB for a summary of the findings from nonclinical studies and known and potential benefits and risks associated with axicabtagene ciloleucel CAR T-cell therapy.

2. OBJECTIVES AND ENDPOINTS

Table 1. Objectives and Endpoints

Primary Objective	Primary Endpoint
• Evaluate the rate and severity of CRS and neurologic events following outpatient administration of axicabtagene ciloleucel	• Incidence rate and severity of CRS and neurologic events
Secondary Objectives	**Secondary Endpoints**
• Characterization of the expanded safety profile including, time to onset and duration of CRS/neurologic events, time to hospitalization, incidence and duration of infections/cytopenias • Change in the European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) over time over time. • Assessment of clinical efficacy • Assessment of pharmacokinetics and pharmacodynamics, including levels of anti-CD19 CAR-T cells and serum pro- inflammatory, immuno-modulatory and effector molecules	• Time to onset and duration of CRS and neurologic events following axicabtagene ciloleucel administration Rates of hospitalization after axicabtagene ciloleucel infusion as measured by proportion of hospitalized subjects within 72 hours, 3 days after infusion date,7 days, 14 days, and 30 days. • Duration of initial hospitalization after axicabtagene ciloleucel infusion • Proportion of ICU admitted subjects • Duration of ICU admission during first hospitalization after axicabtagene ciloleucel infusion • Safety of axicabtagene ciloleucel as measured by the incidence of AEs and SAEs • Change of EQ-5D-5L from Baseline to Month 6 • Efficacy of axicabtagene ciloleucel as measured by ORR, CR rate, DOR, PFS, EFS (all per investigator assessment), and OS • Blood levels of key serum analytes (including cytokines, defined in Section 5.27), and axicabtagene ciloleucel CAR T-cells over time
Exploratory Objectives	**Exploratory Endpoints**
• Explore the pattern of worsening of CRS and neurological events following axicabtagene ciloleucel administration (ie, time from initial event grade to higher grade) • Exploration of the utility of electronic wearable technology in outpatient monitoring and assessment of predictive modeling for outpatient selection for axicabtagene ciloleucel treatment	• Time from end of axicabtagene ciloleucel infusion to: — Initial CRS and progression to higher grade CRS — Initial neurologic events, and progression to higher grade neurologic events — Tocilizumab administration — Corticosteroid administration (aside from prophylactic dexamethasone per protocol) — Administration of vasopressors — Administration of supplemental oxygen for documented hypoxemia

	• Number of urgent care/ED visits and/or unscheduled outpatient visits with/without subsequent hospital admission • Cumulative use of corticosteroids and other concomitant medications of interest • Phenotypes and functional attributes of pre-infusion axicabtagene ciloleucel (product characterization) • Extended characterization of serum and plasma analytes and association with clinical outcome

3. STUDY DESIGN

For study requirements, refer to the schedule of assessments (SOA Table 7 and Table 8). A study schema is provided in Figure 1.

3.1. Study Design

This Study KT-US-482-0137 is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with r/r LBCL in the outpatient setting.

Approximately 30 subjects will be enrolled in this Phase 2 study.

The 28-day screening period begins on the date the subject signs the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) and continues through confirmation of enrollment (ie, commencement of leukapheresis), or until the subject withdraws consent before enrollment, or it is determined that the subject is a screen failure (ie, does not meet the eligibility criteria per Section 4.2). Study sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled, or the reason why the subject failed screening. These data will be entered in the electronic case report form (eCRF).

Informed consent must be obtained before completion of any nonstandard-of-care, study-specific procedures. Procedures that are part of the standard of care are not considered study-specific procedures and may be performed before obtaining consent and used to confirm eligibility.

A subject is considered enrolled in the study at commencement of leukapheresis. Subjects must have undergone screening procedures and their results must have been confirmed to meet the study eligibility criteria (Section 4.2) at screening. For laboratory tests performed after screening and before initiation of leukapheresis, allowance will be made for expected normal variation of within 5% of laboratory test value cutoffs noted in the inclusion criteria. If there is a need for a subject to have leukapheresis repeated, they must continue to meet the study eligibility criteria (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria) before the leukapheresis procedure is performed.

After enrollment/leukapheresis, subjects may undergo optional bridging therapy at investigator discretion (Section 5.4).

After enrollment/leukapheresis and before initiation of lymphodepleting (conditioning) chemotherapy, subjects and family caregivers are required to be educated on taking vital signs in an outpatient setting, symptoms and signs of CRS and neurologic events, and the outpatient monitoring schedule.

Subjects will then undergo conditioning/lymphodepleting chemotherapy with fludarabine 30mg/m^2/day and cyclophosphamide 500mg/m^2/day for 3 consecutive days from Day -5 to Day -3 (see Section 5.5 for details), followed by prophylactic corticosteroid treatment with 10 mg dexamethasone, administered daily on Day 0, Day 1, and Day 2.

On Day 0 (following dexamethasone 10 mg), all subjects will receive a single infusion of axicabtagene ciloleucel at the target dose of 2 X 10^6 cells/kg without being hospitalized. Subjects will stay in close proximity (2-hours travel distance) of the study site for at least 4 weeks after axi-cel infusion, with immediate access to care by the investigator and/or the treating team. Please refer to Section 5.6.3 for the outpatient monitoring schedule and admission criteria.

After completing the axicabtagene ciloleucel infusion, all subjects will be followed in the outpatient setting for 14 days during the post-treatment assessment period. Starting from Day 0 (the day of axicabtagene ciloleucel infusion), subjects will return to the clinic for evaluation at Week 4, Month 2, and Month 3.

Upon completion of the post-treatment assessment period, subjects will enter the long-term follow-up (LTFU) period. Subjects who complete approximately 18 months of follow-up will be transitioned to a LTFU study (KT-US-982-5968). If the study is terminated early, all subjects who were infused with axicabtagene ciloleucel will be transitioned to KT-US-982-5968 at the time of study termination.

3.1.1. Rationale for Study Design Elements

3.1.1.1. Rationale for Dose and Route of Administration of Axicabtagene Ciloleucel

The rationale for the axicabtagene ciloleucel dose in this study is based on the aggregate safety and efficacy data observed in ZUMA-7, as outlined in the IB. Based on the favorable benefit/risk ratio seen in ZUMA-7, axicabtagene ciloleucel will be administered at a target dose of 2 x 10^6 anti-CD19 CAR-T cells/kg intravenously (IV).

3.1.1.2. Rationale for Lymphodepleting Chemotherapy

Before administration of axicabtagene ciloleucel, subjects will receive a nonmyeloablative lymphodepleting regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo. Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide and fludarabine beginning on Days −5 through Day −3.

Increasing levels of lymphodepleting chemotherapy have been shown to correlate with clinical response to adoptive cellular therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in nonclinical models. The depth and duration of lymphodepletion in nonclinical models correlate 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 regulatory T-cells, or enhancing antigen-presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine are an effective lymphodepleting regimen.

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent that also possesses potent immunosuppressive activity. Fludarabine phosphate is a synthetic purine antagonist antimetabolite.

Administration of cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) for 3 consecutive days has been studied and tolerated in subjects with B-cell malignancies. This regimen has been evaluated at the National Cancer Institute (NCI) and is the dose of lymphodepleting chemotherapy that is being used in other studies at Kite Pharma, Inc. (hereafter referred to as Kite).

3.1.1.3. Rationale for Corticosteroid Therapy

The ZUMA-1 Phase 2 safety management Cohorts 3 through 6 are exploring interventions to reduce the incidence of severe CRS and neurologic toxicity in subjects with r/r NHL treated with axicabtagene ciloleucel. The design of these cohorts explored different options as methods to reduce severe toxicity. Cohort 6 used prophylactic corticosteroids in conjunction with the same earlier interventions used in Cohort 4. The primary objective of Cohort 6 was to assess the impact of prophylactic corticosteroid use and earlier interventions on the incidence and severity of CRS and neurologic toxicities.

Cohort 6 of ZUMA-1 was intended to assess whether prophylactic corticosteroid use and earlier intervention with corticosteroids and/or tocilizumab could reduce the incidence and severity of CRS and neurologic events. The cohort enrolled and treated 40 subjects with aggressive LBCL, comprising 24 subjects (60%) with DLBCL, 9 subjects (23%) with TFL, and 7 subjects (18%) with HGBL.

Prophylactic corticosteroids were administered to all 40 subjects; 25 subjects also received corticosteroids for toxicity management, and 23 subjects also received tocilizumab.

Safety was assessed among all 40 treated subjects. Thirty-two subjects (80%) had CRS. Notably, the incidence of Grade 3 or higher CRS was 0% in Cohort 6 primary analysis relative to 13% in the primary analysis of ZUMA-1 Cohorts 1 and 2. The incidence, severity and duration of CRS appears to be decreased in Cohort 6 relative to Cohorts 1 and 2, and the time to onset was delayed. In the Cohort 6 12-month analysis, there were no changes from the 6-month analysis.

The incidence of severe neurologic toxicities was numerically lower in 6-month analysis of Cohort 6 relative to the 6-month analysis of Cohorts 1 and 2, whereas the time to onset was similar and the duration was numerically longer for Cohort 6 versus Cohorts 1 and 2.

Efficacy was also assessed, and it was based on the investigator's assessment of response for all treated subjects. The ORR per investigator assessment was 95%, with a CR rate of 80%.

The study results supported prophylactic corticosteroid use and earlier interventions for toxicity management appeared to improve the overall benefit:risk profile for axicabtagene ciloleucel without compromising efficacy. The benefit of prophylactic corticosteroids and earlier interventions for the management of CRS and neurologic toxicity observed in Cohort 6 are supported mechanistically by pharmacokinetic and pharmacodynamic evaluation showing comparable CAR T-cell expansion in blood and reduced levels of selected serum inflammatory markers for subjects in Cohort 6 relative to Cohorts 1 and 2.

3.2. Rationale for Retreatment

Allowance for retreatment is based on clinical experience in ZUMA-1 study, 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, 6 of 10 retreated subjects had a partial response (PR) or CR to the retreatment. The subject 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 as of the data cutoff date.

In ZUMA-7, 9 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.

3.3. Duration of Subject Participation

The duration of the study for each subject will be approximately 18 months and will vary depending on a subject's screening requirements, response to treatment, survival, and timing of transition to the separate study, KT-US-982-5968, for long-term follow-up (LTFU) (discussed in Section 3.4 and Section 3.7).

For a subject who completes participation in this study and also completes the LTFU period in KT-US-982-5968 study, the entire duration of a subject's participation in both studies will be up to approximately 15 years from the time of 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 AEs that could be the potential consequence of this emerging technology.

3.4. End-of-study Definition

The end-of-study for each subject is defined as when the subject completes the Month 18 visit or, is considered lost to follow-up, withdraws consent, or dies.

At the end of study, each subject will transition to the KT-US-982-5968 study.

3.5. Subsequent Anticancer Therapy

Subsequent anticancer therapy should not be administered unless a subject's disease progression has been documented and confirmed. Subsequent anticancer therapy refers to treatment administered after the axicabtagene ciloleucel infusion that is necessary to treat a subject's disease, such as non-study-specified chemotherapy, immunotherapy, targeted agents, stem cell transplant (SCT), radiation therapy, high-dose corticosteroids (other than those defined/allowed in this protocol), and other investigational agents.

Consolidation therapy or maintenance therapy that is not intended to treat disease progression will not be counted as a subsequent anticancer therapy.

Subsequent anticancer therapy administered after the axicabtagene ciloleucel infusion for a subject's disease will be recorded in the eCRF for this study for all enrolled subjects until the end of this study (defined in Section 3.4) or, while still a participant in this study, the subject is considered lost to follow-up, withdraws consent, or dies.

For subjects who are enrolled but do not receive the axicabtagene ciloleucel infusion, information about any additional anticancer therapy will also be collected until the end of this study (defined in Section 3.4) or, while still a participant in this study, the subject is considered lost to follow up, withdraws consent, or dies.

3.6. Instructions for Follow-up and Data to be Collected for Subjects Withdrawn From Treatment/Study

If partial withdrawal of consent occurs (defined in Section 4.3), the investigator must discuss with the subject the appropriate process for discontinuation from study treatment or other study-specific procedures and must discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA (Table 7 and Table 8).

The level of follow-up and method of communication should also be discussed between the research staff and subject and documented in the source documents.

If withdrawal of full consent occurs (defined in Section 4.3), the investigator is to discuss with the subject appropriate procedures for withdrawal from the study. If a subject withdraws full consent, the subject data collected up to withdrawal of consent will be retained and included in the analysis of the study and, where permitted by local regulations, publicly available data (eg, death records) can be included after withdrawal of consent.

As part of the study, study sites may be asked to conduct searches of public records such as those establishing survival status (eg, for subjects lost to follow-up), if available, to obtain survival data for any subject for whom the survival status is not known, per the applicable local laws. Sites may also be asked to retrieve autopsy reports to confirm status of disease at the time of death, if possible, per the local laws.

3.7. Long-term Follow-up

After completing at least 18 months of assessments in this study since the initial axicabtagene ciloleucel infusion, and after agreement by the Sponsor, subjects will be transitioned to a separate LTFU study (KT-US-982-5968). Subjects will be monitored for occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to axicabtagene ciloleucel; presence of replication-competent retrovirus (RCR); and height, weight, and sexual maturation (pediatric and adolescent subjects only) for up to 15 years from the time of the initial axicabtagene ciloleucel infusion (refer also to Section 11.2). In the LTFU study, subjects will continue assessments at time points contiguous with their time point in this study.

If the study is terminated early, all subjects who were infused with axicabtagene ciloleucel will be transitioned to the LTFU study, KT-US-982-5968, at the time of study termination.

3.8. Criteria to Stop Enrollment

The safety review team (SRT) can make a recommendation to the sponsor to stop enrollment early if unacceptable safety risk related to outpatient dosing is identified based on the guidelines in the SRT charter. Refer to Section 7.9 (SRT) for more information.

3.9. Number of Participating Study Sites

Approximately 20 study sites located in the US will participate in this study. During the conduct of the study, additional regions, countries, or study sites may be added as necessary.

3.10. Source Data

The source data for this study will be obtained from original documents/records including central laboratory, local laboratory, specialty laboratory (for pharmacokinetics and/or pharmacodynamics data), and/or medical record data.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 30 subjects will be enrolled and treated and included in the efficacy evaluable set. Refer to Section 8.6.5.1 for the definition of the efficacy evaluable set.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

To be enrolled in the study, subjects must meet all of the following criteria:

1) Histologically confirmed LBCL, including the following types defined by World Health Organization (WHO) 2016 classification {Swerdlow 2016} by local pathology laboratory assessment, are eligible as defined below:

    a) DLBCL not otherwise specified

    b) HGBL with or without MYC and BCL2 and/or BCL6 rearrangement

    c) DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV) + DLBCL

    d) Primary mediastinal (thymic) LBCL

    e) Primary cutaneous DLBCL, leg type

    f) Transformation of follicular lymphoma to DLBCL will also be included

2) Relapsed or refractory disease after 1 or more lines of therapy

3) Subjects must have received adequate prior therapy including:

    a) Anti-CD20 monoclonal antibody AND

    b) An anthracycline-containing chemotherapy regimen

4) At least 1 measurable lesion according to the Lugano Response Criteria for Malignant Lymphoma {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.

5) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis.

6) Toxicities due to immediate prior therapy must be stable and recovered to Grade ≤ 1 (except for clinically nonsignificant toxicities such as alopecia)

7) Age 18 or older

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

9) Adequate bone marrow function as evidenced by:

   a) Absolute neutrophil count (ANC) ≥ 1000/uL

   b) Platelets ≥ 75,000/uL

   c) Absolute lymphocyte count ≥ 100/uL

10) Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by:

   a) Creatinine clearance (eg, Cockcroft Gault) ≥ 60 mL/min

   b) Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 upper limit of normal (ULN)

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

   d) Cardiac ejection fraction ≥ 50%, and no evidence of pericardial effusion (except trace or physiological) as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings. Multiple-gated acquisition (MUGA) scan may be used if an ECHO is not available at the site.

   e) No clinically significant pleural effusion or ascites (Grade 1 per CTCAE v5.0)

   f) Baseline oxygen saturation, (sPO_2) > 92% on room air

11) Subject agrees to outpatient treatment setting and to adhere to the prespecified clinical monitoring requirements outlined in the SOA

12) 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)

4.2.2. Exclusion Criteria

To be enrolled in the study, subjects must not meet any of the following criteria:

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

2) History of Richter's transformation of chronic leukemic lymphoma (CLL)

3) History of autologous or allogeneic stem cell transplant

4) Prior CD19 targeted therapy

5) Prior chimeric antigen receptor (CAR) therapy or other genetically modified T-cell therapy

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

7) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite medical monitor.

8) Known history of human immunodeficiency virus (HIV) infection, hepatitis B (HBsAg positive) or hepatitis C (anti-HCV positive) infection. A history of hepatitis B or hepatitis C infection is permitted if the viral load is undetectable per quantitative polymerase chain reaction and/or nucleic acid testing.

9) 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 catheter such as a Port-a-Cath or Hickman catheter are permitted

10) Subjects with detectable cerebrospinal fluid (CSF) malignant cells, brain metastases, or with a history of central nervous system (CNS) lymphoma or primary CNS lymphoma. DLBCL epidural involvement should be considered as positive CNS disease

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

12) Subjects with cardiac lymphoma involvement

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

14) Requirement for urgent therapy within 6 weeks before enrollment due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

15) Primary immunodeficiency

16) History of autoimmune disease (eg, Crohn's, rheumatoid arthritis, systemic lupus) requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years

17) History of symptomatic deep vein thrombosis or pulmonary embolism requiring therapeutic anticoagulation within 6 months before enrollment. History of upper extremity line related deep vein thrombosis (DVT) within 3 months of lymphodepleting (conditioning) chemotherapy

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

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

20) Live vaccine ≤ 6 weeks before planned start of conditioning regimen

21) Women of child-bearing 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.

22) Subjects who are not willing to practice birth control from the time of consent through 6 months after axicabtagene ciloleucel infusion

23) 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

4.3. 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 receiving protocol-required treatment and/or other study-specific procedures at any time during the study but continue to participate in certain follow-up elements of the study. This is referred to as partial withdrawal of consent.

Withdrawal of full consent from the study means that the subject does not wish to receive further protocol-required treatment or undergo study-specific procedures, and the subject does not wish to continue further study follow-up. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

4.3.1. Reasons for Removal From Treatment

Reasons for removal of a subject from the protocol-required treatment include any of the following:

- AE
- Withdrawal by subject
- Product not available
- Lost to follow-up
- Death
- Termination of the study by the sponsor
- Other (eg, investigator decision or noncompliance)

4.3.2. Reasons for Removal From Study

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

- Withdrawal by subject
- Lost to follow-up
- Death
- Termination of the study by the sponsor
- Other (eg, investigator decision or noncompliance)

4.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects is attained in the efficacy evaluable set. Refer to Section 8.6.5.1 for the definition of the efficacy evaluable set.

5. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study at each study period/visit are described in the following sections and will be performed at the time points presented in the SOA (Table 7 and Table 8) in Section 11.2.

The investigator must document any deviation from the protocol procedures and notify Kite or the contract research organization (CRO).

5.1. Subject Informed Consent

Before a prospective subject can participate in the clinical study, the investigator must obtain written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and potential risks. Subjects should sign the most current IRB/IEC-approved ICF before any study -specific activity or procedure is performed. Refer to Section 9.1.3 for more information about the informed consent process.

All subjects who are enrolled in the study should be reconsented with any updated version of the IRB/IEC-approved ICF if relevant to their participation in the study, unless the subject fully withdraws consent from the study, including any follow-up. Subjects who partially withdraw consent should be reconsented with the revised ICF.

5.2. Screening and Subject ID Assignment

Investigative sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on 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 non-standard of care study-specific procedures. Procedures that are part of standard of care are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility. Confirmation of this data must occur within the time allowance as outlined below and in the SOA.

Each subject who enters the screening period will receive a unique subject identification [ID] number before any study-specific procedure or activity is initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject ID number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened, retreated, or enrolled in the LTFU study.

Subjects who fail to meet the eligibility criteria will be allowed to rescreen using the same unique subject ID number. Subjects will perform the assessment that initially resulted in the subject failing screening, including any other procedures that fell outside of the designated screening window (ie, laboratory assessments or positron emission tomography-computed tomography [PET-CT] scans).

Only subjects who meet the eligibility criteria listed in Section 4.2 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 on the subject screening log with the reasons for failing screening.

Refer to the SOA (Table 7) for a listing of study procedures to be completed during the screening period.

5.2.1. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period will be permitted to rescreen. The investigator should consult with the medical monitor about rescreening cases. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days after signing of the original ICF, the assessment or procedure that initially resulted in the subject failing screening will be performed, including any other procedures that fell outside of the designated screening window (eg, laboratory assessments); all other initial screening procedures/assessments do not need to be repeated. If rescreening occurs or leukapheresis is delayed more than 28 days after the signing of the original ICF, the subject must be reconsented and all screening procedures/assessments must be repeated.

5.3. Leukapheresis

Before leukapheresis commences, the following criteria must be met:

- In general, all criteria that were confirmed during screening for eligibility must not be known to be violated before leukapheresis, Additionally, the investigator must review and confirm that the last complete blood count (CBC) with differential and chemistry panel results from the blood draw before the start of leukapheresis meet the criteria detailed in inclusion criterion ±5%. If any screening assessments or procedures are repeated between confirmation of eligibility and the start of leukapheresis and the results are outside the criteria listed in Section 4.2 (or outside ±5% of the laboratory test value cutoffs noted in the inclusion criteria), the subject should not be leukapheresed, and the Kite medical monitor must be consulted.

- Subjects must have no evidence of clinically significant infection before leukapheresis. Should a subject have clinically significant infection immediately before leukapheresis, cell collection must be delayed until the event resolves.

- If leukapheresis is delayed > 5 days after eligibility confirmation, a complete blood count (CBC) with differential and chemistry panel must be repeated.

- If the white blood cell (WBC) count from a sample collected at the time of leukapheresis is ≥ 20,000 cells/µL, the Kite medical monitor must be consulted before proceeding with leukapheresis.

- 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 before leukapheresis (refer to Section 6.5).

After the above criteria are met, mononuclear cells will be obtained by leukapheresis (12 to 15 liter apheresis 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 Investigational Product Manual (IPM).

Refer to the SOA (Table 7) for a listing of study procedures to be completed during the leukapheresis visit.

In the event of a manufacturing failure of the CAR T-cell product (eg, the planned number of CAR-T cells is not reached or there are observations affecting product safety), the leukapheresis procedure may be repeated.

Prior to initiation of axicabtagene ciloleucel infusion, subjects and family caregivers should receive additional education on potential signs and symptoms of CRS, neurological toxicity, outpatient monitoring schedule and other guidelines including criteria for contacting the treating team for hospital admission per institutional guideline. Subjects and family caregivers will be required to stay within a 2-hours travel distance from the treatment center for at least 4 weeks after axicabtagene ciloleucel infusion.

5.4. Bridging Therapy (Optional)

At the discretion of the investigator, bridging therapy, may be administered after leukapheresis and no later than 7 days before initiating lymphodepleting chemotherapy

Subjects who received bridging therapy must have a tumor assessment after bridging therapy to ensure presence of measurable disease.

5.5. Lymphodepleting (Conditioning) Chemotherapy)

The lymphodepleting chemotherapy regimen will consist of cyclophosphamide 500 mg/m^2/day IV infused over approximately 60 minutes on Days −5, −4, and −3; and fludarabine 30 mg/m^2/day IV over approximately 30 minutes on Days −5, −4, and −3.

Any consideration for changes in the dose for the lymphodepleting chemotherapy should be discussed with the Kite medical monitor.

Lymphodepleting chemotherapy will be administered on Days −5 through −3 before administration of axicabtagene ciloleucel to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel T-cells in vivo. Refer to Section 3.1.1.2 for additional information about the rationale for administration of lymphodepleting chemotherapy.

Electronic wearable devices will be deployed as detailed in Section 6.7 and subjects will receive additional instructions. Investigator site staff will check devices for proper functioning on Days -5, -4 and -3.

5.5.1. Requirements for Initiating Lymphodepleting Chemotherapy

Administration of axicabtagene ciloleucel cells to subjects with ongoing infection or inflammation, even if subjects are asymptomatic, may increase the risk of high-grade and fatal toxicity. All efforts should be made to rule out such conditions before both lymphodepleting chemotherapy and cell infusion. If any of the following criteria are met before initiation of lymphodepleting chemotherapy, the work up listed in Section 5.5.1 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38ºC within 72 hours before lymphodepleting chemotherapy
- C-reactive protein (CRP) ≥ 100 mg/L any time between enrollment to the start of lymphodepleting chemotherapy
- WBC count or differential concerning for infectious process between enrollment to the start of lymphodepleting chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with a high percentage of segments/bands)

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of lymphodepleting chemotherapy and the results are outside the eligibility criteria listed in Section 4.2 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), then the condition must resolve before proceeding with lymphodepleting chemotherapy.
- Complete history and physical examination, 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 lymphodepleting chemotherapy (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per an 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).

- The 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 (eg, bacterial, 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 (or after discussion with the medical monitor for extenuating circumstances), the subject can proceed with lymphodepleting chemotherapy.

5.6. Axicabtagene Ciloleucel

Axicabtagene ciloleucel treatment will consist of a single infusion of CAR-transduced autologous T-cells administered intravenously on Day 0 at a target dose of 2 X 10^6 cells/kg intravenously.

All subjects will receive axicabtagene ciloleucel infusion without being hospitalized. However, all subjects need to stay in a close proximity (2-hours travel distance) of the study site for at least 4 weeks after axi-cel infusion with immediate access to urgent care by the investigator and/or treating team. All subjects need to follow the schedule of assessments especially in the first 2 weeks of axicabtagene ciloleucel infusion (Table 7).

Instructions associated with administration of axicabtagene ciloleucel are provided in Section 6.3.

5.6.1. Requirements for Axicabtagene Ciloleucel Infusion

Central venous access, such as a port or peripherally inserted central catheter, is required for administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed.

Axicabtagene ciloleucel is a subject-specific product, and the product must not be infused if the information on the subject-specific label does not match the intended subject's information (eg, subject ID number). The volume of axicabtagene ciloleucel infused, thaw start/stop time, and axicabtagene ciloleucel administration start/stop time must all be noted in the subject's medical record. The product must not be thawed until the subject is ready for the infusion.

Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the IPM. The IPM must be reviewed before administration of axicabtagene ciloleucel. Study sites should follow institutional guidelines for the infusion of cell products.

If any of the following criteria are met before initiation of the axicabtagene ciloleucel infusion, the work-up listed below must be performed to determine the potential cause if there is no identified source of infection:

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

Additionally:

- All eligibility criteria listed in Section 4.2 of the protocol must remain confirmed before treatment with axicabtagene ciloleucel, except that laboratory test values can be within 5% of the cutoffs noted in the inclusion criteria. If any screening assessments or procedures are repeated after subject enrollment and the start of the axicabtagene ciloleucel infusion and the results do not meet the criteria listed in Section 4.2 (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria), the condition must resolve before proceeding with the axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by lymphodepleting chemotherapy).
- Complete history and physical examination 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 infusion of axicabtagene ciloleucel (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per an 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).
- The 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 (eg, bacterial, PCR, stool studies, or imaging studies) must be negative. If there is clinical suspicion of 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, and/or after discussion with the medical monitor for extenuating circumstances, the subject can proceed with administration of axicabtagene ciloleucel, following the procedures described in Section 5.6.2 and Table 7.

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy (refer to Section 5.5).

5.6.2. Axicabtagene Ciloleucel Premedications (Day 0)

The following pre- axicabtagene ciloleucel infusion medications should be administered approximately 1 hour before infusion of axicabtagene ciloleucel.

- Acetaminophen 650 mg orally (PO) or equivalent
- Diphenhydramine 12.5 mg administered either orally or via IV or equivalent

5.6.2.1. Prophylactic Corticosteroids

Subjects will be administered dexamethasone 10 mg orally (PO) or IV daily on Day 0 (prior to axicabtagene ciloleucel infusion), Day 1, and Day 2.

5.6.3. Monitoring After Axicabtagene Ciloleucel Infusion

Subjects will be monitored daily at a healthcare facility for at least 7 days after the axicabtagene ciloleucel infusion for toxicity, including signs and symptoms of CRS and neurologic events. In addition, the assessments described in the SOA (Table 7) will be performed during this period.

Institution can provide thermometer, blood pressure cuff, and pulse oximeter, to their subjects and care givers for the self-measurement of temperature, HR, RR, BP, oxygen saturation (sPO_2) per their local standard practice.

Daily Monitoring Guideline is described in detail below:

5.6.3.1. Day 0

Subjects will report to the clinic in the morning (eg, 8:00 AM) for evaluation. Complete baseline physical exam including baseline temperature, BP, HR, RR and sPO_2, as well as neurological evaluation will be performed and recorded. Additionally, laboratory tests (refer to SOA for required laboratory draws) will be performed.

If there are no contraindications to proceed with axicabtagene ciloleucel, prophylactic dexamethasone 10 mg IV/PO will be administered prior to axicabtagene ciloleucel infusion.

Axicabtagene ciloleucel will be infused in the outpatient clinic and subjects are to be monitored post-infusion according to institutional guidelines. A complete set of vital signs (temperature, HR, RR, BP, sPO_2) and neurological assessment should be obtained according to institutional guidelines and as needed during waking hours. Subjects and caregivers should notify the clinic

and/or the on-call line if there are any prespecified and/or new abnormalities when outside the hospital setting. An optional telemedicine visit may occur at the end of the day (e.g. 22:00) with the on-call treating team to review the vital signs for the day, perform a new vital signs check, and conduct neurological assessments.

Electronic wearable device will be checked by the investigator site staff for proper functioning.

5.6.3.2. Day 1 to 7

Subjects will report to the outpatient clinic in AM (eg, 8:00 AM) for the following:

- Overnight events and the vital signs logbook, if used, from Day prior will be reviewed
- Electronic wearable device will be checked.
- A complete physical examination, vital signs (temperature, BP, HR, RR and sPO_2), and neurological assessment will be obtained.
- On Days 1 and 2, dexamethasone 10 mg IV/PO will be administered.
- Any laboratory sample collection required (referred to SOA) will be performed.

If no criteria for admission is met, subjects may be discharged from clinic per local standards. While away from clinic, a complete set of vital signs (temperature, HR, RR, BP, sPO_2) and neurological assessment should be monitored according to institutional guidelines and as needed during waking hours. Subjects and caregivers should notify the clinic and/or the on- call line if there are any prespecified and/or new abnormalities observed when outside of the hospital setting. An optional telemedicine visit may occur at end of day (e.g. 22:00) with the on-call treating team to review the vital signs for the day, complete a set of new vital signs, and neurological assessment.

5.6.3.3. Guidelines for Hospitalization:

CRS, any grade

Neurological event, any grade

Other criteria at the discretion of the covering physician.

For Grade 1 and 2 CRS (eg, fevers, hypotension responsive to fluids, hypoxia responsive to O_2 (nasal canula) and Grade 1 neurologic events, subjects may be admitted for outpatient observation depending on the discretion of the physician. If symptoms persist for longer than 8 hours and /or recur within 24 hours, subject should be admitted to the inpatient setting for closer monitoring and evaluation.

After 7 days of daily outpatient monitoring, subjects may be allowed to follow up at longer intervals per investigator's discretion. Subjects should return to clinic for a follow up visit at minimum at the specified intervals as outlined in Table 7. All subjects should remain within proximity of the study site (within a 2-hours travel distance) for at least 4 weeks after the axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be reminded on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, 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 Section 6.4 and Section 6.5 for descriptions of medications that should not be taken before and after the axicabtagene ciloleucel infusion.

5.6.4. Retreatment with Axicabtagene Ciloleucel

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 same study procedure requirements that were followed during his or her initial course of treatment.

Refer to the SOA (Table 7) for a listing of study procedures to be completed during the axicabtagene ciloleucel treatment period.

The allowance for retreatment includes the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel, as well as administration of a second course of lymphodepleting chemotherapy before retreatment with axicabtagene ciloleucel.

The following criteria must be met in order to be considered for a repeat course of therapy:

- Subjects who achieved a PR or CR and subsequently experience disease progression may have an option to receive a second course of lymphodepleting (conditioning) chemotherapy and axicabtagene ciloleucel.
- CD19 tumor expression confirmed locally by immunohistochemistry or flow cytometry on a representative progression biopsy. A portion of the biopsy should be sent to the central laboratory if possible.
- Subject continues to meet the original study eligibility criteria with exception of prior axicabtagene ciloleucel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.
- Subject has not received subsequent therapy for the treatment of LBCL
- Subject did not experience a life-threatening toxicity related to axicabtagene ciloleucel during the original course of treatment

- Toxicities related to lymphodepleting chemotherapy (fludarabine and cyclophosphamide), with the exception of clinically insignificant toxicities (eg, alopecia), have resolved to severity of Grade 1 or lower or returned to baseline before retreatment

- Subject does not have known axicabtagene ciloleucel neutralizing antibodies (exception: if a non-neutralizing axicabtagene ciloleucel antibody develops, subjects may be retreated if they meet the original study eligibility criteria)

The decision to administer retreatment should be made in consultation with the Kite medical monitor. In addition, a discussion regarding the benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel should occur with the subject before performing any study-related procedures or treatment. The second dose could be manufactured at the same time that the first axicabtagene ciloleucel is made with existing cryopreserved peripheral blood mononuclear cells (PBMCs).

Alternatively, the subject may need to undergo a second leukapheresis and should be informed of this possibility. This conversation should also be recorded in the subject's source document.

Subjects may only be retreated once. Subjects who are retreated will follow the same treatment schedule and dosing and procedural requirements per the initial treatment.

5.7. Demographic Data

Demographic data will be collected for each subject as per country and local regulations and guidelines. Where applicable, demographic data will include sex, date of birth, race, ethnicity, and country of enrollment with the intent to assess the possible association of demographics with subject safety and treatment effectiveness.

5.8. Medical and Treatment History

Relevant medical history before the start of AE reporting (ie, from before enrollment [leukapheresis]) will be collected at screening. Relevant medical history is defined as data about the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the eCRFs.

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

5.9. Physical Examination

Physical examinations will be performed at screening and at the time points noted in the SOA (Table 7 and Table 8).

Clinically significant adverse changes (as determined by the investigator) when compared with the baseline examination will be reported as AEs.

5.10. Weight and Height

Weight (plus height at screening) will be collected at screening and at the time points noted in the SOA (Table 7 and Table 8).

5.11. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at times outlined in the SOA and as outlined in the outpatient monitoring guideline (Section 5.6.3).

During any inpatient hospitalization, vital signs are recommended at least every 6 hours or more frequently as clinically indicated.

5.12. ECOG Performance Status

Performance status as measured by the ECOG scale will be performed at the time points specified in the SOA (Table 7) to quantify the subject's general well-being and ability to perform activities of daily life.

5.13. Neurological Examination

The neurologic examination will include a cognition assessment: and will be performed daily during outpatient visit for 7 days following axicabtagene ciloleucel infusion. A neurological examination will be performed with any abnormalities of the following 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, neuropsychological findings (eg, speech, cognition and emotion). A neurological assessment (which may include the Mini-Mental Status Exam [MMSE]) should be done prior to axicabtagene ciloleucel infusion on treatment Day 0, then continue daily during the 7 day out patient monitoring period.

Subjects and family will be specifically queried for neurological symptoms observed in the interval since the last baseline neurological examination.

Neurologic examinations will be performed according to the time points specified in the SOA (Table 7).

The subject's neurological status will be evaluated at screening to establish a baseline. Evaluations of neurological status will be assessed according to the time points specified in the SOA (Table 7). Changes in neurological status should be reported as an AE if considered clinically significant at the discretion of the investigator.

5.14. Cardiac Function

5.14.1. Echocardiogram

Each subject's cardiac function, as measured by left ventricular ejection function (LVEF) will be assessed by an ECHO or MUGA, at screening to confirm study eligibility. No evidence of clinically significant pericardial effusion, as required by eligibility, will also be confirmed by ECHO.

If the last chemotherapy regimen the subject received is not considered cardiotoxic, an ECHO performed within 28 days before signing the ICF may be used for eligibility. If the last chemotherapy regimen the subject received is considered cardiotoxic, then an ECHO performed after the subject received their last chemotherapy treatment and within 28 days before signing the ICF may be used for confirmation of eligibility.

5.14.2. Electrocardiogram

To establish a baseline, a 12-lead ECG will be performed at screening. ECG assessments will include PR duration, QRS duration, QT duration, and RR duration, and corrected QT (QTc) interval.

5.15. Brain MRI/Imaging

Screening:

- Each subject will undergo a screening brain MRI to rule out central nervous system (CNS) metastasis during the screening period of the study. The MRI will be performed with contrast whenever possible.

- The MRI should be performed as close to enrollment/leukapheresis as possible and within 28 days before leukapheresis for eligibility. An MRI collected as standard of care within this timeframe is acceptable.

- In case of contraindication, to MRI the subject may choose to undergo a CT of the brain with contrast, as an alternative.

After the Infusion:

- 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 examination, will have a brain MRI for examination of cerebrospinal fluid (CSF).

Refer to the current IB for radiological examination to be performed as part of the evaluation of any new onset of neurologic events of severity Grade 2 or higher.

5.16. Lumbar Puncture

Analytes and immune cell subsets from CSF will be analyzed by the central laboratory.

Lumbar puncture will be performed at the time points specified in the SOA (Table 7). Opening pressures should be measured with each lumbar puncture when possible and recorded in the subject's site chart.

- Screening: 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 CSF for possible CNS involvement, will have a lumbar puncture at screening for examination of CSF to determine the presence of CNS malignancy. CSF samples will be analyzed at the local laboratory; any remaining material will be sent to the central laboratory for assessment of analytes.
- After the Infusion: Subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion will have lumbar puncture performed to assess CSF, unless contraindicated. Measurement of the opening pressure should be done, when possible, with recording of the results in the subject site chart.
- In addition, subjects who sign the optional portion of the consent will have lumbar puncture for the collection of CSF performed at baseline before axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion (Day 5 ±2 days and Week 4 ±3 days) and sent to the central laboratory.

5.17. Bone Marrow Biopsy/Aspirate

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 can be determined upon initial diagnosis of disease or if negative or unknown at initial diagnosis, at the time of relapse from first-line therapy. If bone marrow involvement was not evaluated at the time of relapse and within 28 days of study entry, a PET-CT and/or bone marrow biopsy and aspirate will be performed to establish a baseline.

If there is evidence of bone marrow involvement at baseline, or if there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy (if PET-CT is not available) will be performed in subjects who are being assessed for CR in order to confirm complete response. The bone marrow aspirate and biopsy must show no evidence of disease by morphology or, if indeterminate by morphology, it must be negative by immunohistochemistry. Refer to Section 11.4.1 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}.

As applicable, bone marrow biopsy/aspirate will be performed to confirm response and a portion will be sent to the central laboratory (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities after axicabtagene ciloleucel.

Refer to Section 11.4 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}. Bone marrow aspirate and biopsies will be analyzed by the investigator at the local laboratory.

Screening/Baseline:

- For fluorodeoxyglucose (FDG)-avid lymphoma, a subject's bone marrow involvement should be assessed by PET-diagnostic CT (refer to Section 5.19) or bone marrow aspirate and biopsy before enrollment or at screening.

Disease/Response Assessment:

- If there is evidence of baseline bone marrow involvement, the PET-diagnostic CT is not available, the lymphoma is not FDG-avid, or 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 complete response/remission (CR) in order to confirm CR {Cheson 2014}. If performed, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or, if indeterminate by morphology, must be negative by immunohistochemistry.

5.18. Archival and Fresh Tumor Biopsy

Archival formalin-fixed paraffin embedded (FFPE) tissue block and/or unstained slides used for the original diagnosis of disease or fresh biopsy (if available) should be submitted to the central laboratory along with the pathology report In addition, a fresh tumor sample will be collected after axicabtagene ciloleucel infusion from subjects who sign the optional portion of consent. Archived tumor samples will be submitted to central laboratory after eligibility has been confirmed and prior to start of lymphodepleting (conditioning) chemotherapy. Post treatment fresh tumor samples (if applicable) will be collected/submitted on Day 5 (± 2 days).

5.19. Positron Emission Tomography-diagnostic CT Scans

Screening fluorodeoxyglucose (FDG)-PET from skull base to mid-thighs and 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, are required to confirm eligibility and to establish a baseline, which must be performed within 28 days prior to enrollment and as close to the enrollment date as possible. Subjects will have their first post-treatment planned PET-CT tumor assessment at Week 4.

Subjects' disease will further be assessed and at regular intervals as highlighted in the SOA during the post treatment and long-term follow-up portion of the study. PET-CTs will continue through Month 18 or until change in lymphoma therapy or disease progression, whichever comes first. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA. 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 time point, assessment should include and may be affected by the PET-CT assessment at the prior time point.

For all PET-diagnostic CT scans:

- The CT must be of diagnostic quality with IV-iodinated contrast, performed by either of the following modalities, depending on the site's capability:
  - as part of a combined PET-diagnostic CT; or
  - as a separate diagnostic quality CT (with IV-iodinated contrast)
- The PET-diagnostic CT scan must include the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease.
- If IV-iodinated contrast is contraindicated per the investigator, then the diagnostic CT scan can use non-iodinated contrast. If non-iodinated contrast is not available or not recommended by the investigator, then the diagnostic CT can be nonenhanced and/or MRI if clinically appropriate.

Screening/Baseline:

- To confirm eligibility and/or to establish baseline PET-diagnostic CT (neck-chest-abdomen-pelvis)/disease assessment) scans are required at screening.
- PET-diagnostic CT scans should be completed as close to enrollment as possible and within 28 days before leukapheresis for eligibility, with the following clarifications:
  - A PET-diagnostic CT scan performed after the subject's last line of therapy and before signing of the ICF may be used for confirmation of eligibility if <28 days before enrollment and no other anticancer treatment has been administered, it may be used for confirmation of eligibility and to establish baseline.
  - If a PET-diagnostic CT scan is performed >28 days prior to the initiation of lymphodepleting (conditioning) chemotherapy or if subject receives any anticancer therapy between screening and lymphodepleting (conditioning) chemotherapy, baseline scans must be repeated.

Disease Assessment:

- The PET-diagnostic CT scans will be performed at the time points outlined in the SOA (Table 7 and Table 9) through Month 18 or until disease progression, whichever comes first. If the subject's disease has not progressed by Month 18, disease assessments will continue to be performed per standard of care. A PET-diagnostic CT scan can be performed at any time disease progression is suspected.

The PET portion of the PET-diagnostic CT scan will be scored per the Deauville 5-point scale. Both the PET and CT portions of the scan will be interpreted according to the Lugano criteria {Cheson 2014}.

If the subject is eligible for retreatment with axicabtagene ciloleucel, the last scan prior to retreatment will be considered the baseline for the purpose of evaluating the response to retreatment.

5.20. EQ-5D-5L

The Euro-QOL, Five Dimensions, Five Levels (EQ-5D-5L) questionnaire is a generic measure of health status captured on the day of assessment that provides a simple descriptive profile and a single index value. The EQ-5D-5L comprises 2 components: a questionnaire covering 5 dimensions and a tariff of values based upon direct valuations of health states using a visual analog scale (VAS). The descriptive questionnaire comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is divided into 5 levels of severity: "no problems", "slight problems", "moderate problems", "severe problems", and "extreme problems".

The EQ-5D-5L VAS is a 20-cm VAS for recording self-rated current health-related quality of life (HRQoL) state and is used to describe the subjects' health status on the day of the assessment. The EQ-5D-5L VAS score is recorded by each subject for his or her current HRQoL state and scored 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

EQ-5D-5L will be scored according to the published administration and scoring manual.

This questionnaire takes approximately 5 minutes to complete. It is expected to be completed by the subject before any procedures are performed, excluding blood draws, and at the time points noted in the SOA (Table 7 and Table 8).

For more information, refer to Section 11.5.1

5.21. Clinical Laboratory Tests

Blood, serum, or urine samples will be collected for clinical laboratory tests for safety assessments at the time points indicated in the SOA (Table 7 and Table 8). Additional samples may be collected as needed for further safety testing. Except for an assay for RCR (performed at the central laboratory), all clinical laboratory test assessments listed in Table 2 will be performed at the local laboratory.

(Note: In addition to collection of blood samples to be sent to the local laboratory for assessment of CBC with differential for clinical/safety evaluation, blood samples will also be collected and sent to the central laboratory at various time points identified in the SOA (Table 7 and Table 8) concomitant with sampling for pharmacokinetic/pharmacodynamics/exploratory assessments).

Table 2. Clinical Laboratory Tests for Safety Assessments

Serum Chemistries (Serum)	Hematology (Blood)	Other (Serum)[G]
Albumin	Absolute lymphocyte count	C-reactive protein[B]
Alanine aminotransferase	CBC with differential[A]	Ferritin[B]
Alkaline phosphatase		Pregnancy test[C]
Aspartate aminotransferase	**PBMCs:**	Serologic testing[D]
Bicarbonate (CO_2) total (as clinically indicated)	RCR[E] (central laboratory)	
Bilirubin total and direct		
Blood urea nitrogen or urea[F]		
Calcium total		
Chloride		
Creatinine		
Creatinine clearance (e.g. estimated by Cockcroft Gault formula)		
Glucose		
Inorganic phosphorus		
Lactate (as clinically indicated)		
Lactate dehydrogenase		
Magnesium total		
Potassium		
Sodium		
Uric acid		

Abbreviations: CAR, chimeric antigen receptor; CBC, complete blood count; EU, European Union; PBMCs, peripheral blood mononuclear cells; RCR, replication-competent retrovirus/; RCL, replication-competent lentivirus.
Notes: All laboratory tests listed above, except for RCR, are performed at the local laboratory.

A. Per institutional guidelines, but CBC with differential must include white blood cell count, neutrophils or absolute neutrophil count, lymphocytes or absolute lymphocyte count, hemoglobin, and platelets. If WBC is too low to provide the differential, this may be omitted.
B. CRP and ferritin will also be tested at the central laboratory as part of the pharmacodynamics evaluation (ie, analytes including cytokines) at the time points listed in the schedule of assessments (Table 7)
C. A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test (β-human chorionic gonadotropin) is positive, the subject should not be enrolled. If a standard-of-care pregnancy test is collected during the course of the study and the result is positive, the investigator should report the pregnancy to Kite per instructions specified in Section 7.8.2.1. If a female partner of a male subject becomes pregnant during the conduct of the study, the pregnancy must be reported to Kite per instructions specified in Section 7.8.2.1.
D. A viral serologic test (eg, HIV, Hepatitis B, and Hepatitis C) will be carried out per institution guidelines and US regulations. Testing may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.
E. Refer to Section 5.25 for information on RCR testing. RCR: collect PBMCs on Day 0 prior to administration of axicabtagene ciloleucel and at Month 3, 6 and 12; then, collected and analyzed yearly for up to 15 years, only if positive at Month 3, 6, or 12, or if RCR is clinically suspected.
F. If the blood urea nitrogen test cannot be analyzed by the local laboratory, urea should be analyzed.
G. If a subject is re-admitted to the hospital during the 7-day observation period with any axicabtagene ciloleucel -related AEs, blood samples for assessment of axicabtagene ciloleucel CAR-T cells and cytokines will be collected on the day of hospital re-admission and then weekly through, and including, the day of discharge. Blood samples for assessment of axicabtagene ciloleucel CAR-T cells and cytokines should also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.

5.22. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating females, and animal reproductive studies have not been performed. This experimental therapy should not be administered to pregnant females or females who are breastfeeding. Females of childbearing potential must have a negative pregnancy test before enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. Females of childbearing potential should be monitored according to local and country-specific regulations. Refer to Section 11.3 for the definition of childbearing potential.

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) through at least 6 months after completing lymphodepleting chemotherapy dosing or axicabtagene ciloleucel administration, whichever is longer. Male subjects are recommended to not father a child for at least 6 months after completing lymphodepleting chemotherapy dosing or axicabtagene ciloleucel administration, whichever is longer. Refer to Section 11.3 for a complete list of highly effective contraception methods.

Refer to Section 7.8.2.1 for reporting instructions for any pregnancy or lactation cases.

Pregnancy testing will occur at the time points indicated in the SOA (Table 7).

5.23. Concomitant Medications/Therapies and Procedures

Information about concomitant medications/therapies and procedures will be collected at the time points specified in the SOA (Table 7 and Table 8). Reporting requirements for concomitant medications are provided in Table 3. Specific concomitant medication collection requirements and instructions are included in the eCRF completion guidelines. Refer to Section 6.4 and Section 6.5 for information about allowed/excluded medications.

Table 3. Reporting Requirements for Concomitant Medications/Therapies and Procedures

Subjects Who Are:		
Not Enrolled (ie, Screen Fails, or Not Leukapheresed)	**Enrolled, but Do Not Receive axicabtagene ciloleucel**	**Enrolled and Receive axicabtagene ciloleucel**
Concomitant therapies related to serious adverse event(s) will be recorded from the date of the signing of the screening ICF through 30 days after the last study-specific screening procedure, respectively.	Concomitant therapies will be recorded from the date of signing of the ICF until 30 days after the last study-specific procedure has occurred (eg, leukapheresis or lymphodepleting chemotherapy) or until the initiation of a new anticancer therapy, whichever occurs first.	• Concomitant therapies, including medications, oxygen, blood products, intubation, and dialysis, will be recorded from the date of signing of the ICF until 3 months after completing treatment with axicabtagene ciloleucel[a]. • After the 3-month follow-up period, targeted concomitant therapies and other medicinal products will be recorded for either 5 years after the axicabtagene ciloleucel infusion[a], or until disease progression or subsequent therapy, whichever occurs first. • Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, vaccinations, and anticancer therapies (eg, chemotherapy, immunotherapy, targeted therapy, hormone therapy, SCT/BMT, high-dose corticosteroids, radiation, surgery, and investigational products).

Abbreviations: BMT, bone marrow transplant; ICF, Informed Consent Form; SCT, stem cell transplant.
a For subjects who are retreated with axicabtagene ciloleucel, the required reporting period will follow the date of the second infusion.

5.24. Survival Data

At the time points identified in the SOA (Table 7 and Table 8), subjects and/or the subject's referring HCP and/or GP may be contacted directly by telephone or email to assess survival status.

5.25. RCR

As KTE-C19 comprises retroviral vector-transduced T-cells, the presence of RCR in the blood of treated subjects will be monitored according to the schedule presented in the SOA (Table 7 and Table 8).

Peripheral blood mononuclear cells (PBMCs) for RCR testing will be collected on Day 0 prior to axicabtagene ciloleucel infusion and at Months 3, 6, and 12. Thereafter, samples will only be collected and tested if an RCR event is clinically suspected and/or a subject tests positive for RCR at any time point within the first year. If the latter, samples/testing will continue per clinical discretion.

If a subject dies of a suspected retrovirus-associated disease or develops a secondary malignancy suspected to be associated with axicabtagene ciloleucel during the study or long-term follow up, a blood sample and tumor biopsy (including any involved bone marrow biopsies) may be obtained and sent to the central laboratory to assay for axicabtagene ciloleucel CAR T cells and/or RCR.

5.26. Levels of CAR-T cells in blood (Pharmacokinetics)

PBMC samples for pharmacokinetic assessments will be drawn according to the schedule presented in the SOA (Table 7). Pharmacokinetic assessments include monitoring of the presence, expansion and persistence of transduced anti-CD19 CAR T cells in the blood over time by droplet digital polymerase chain reaction (ddPCR) analysis.

5.27. Serum analytes (Pharmacodynamic Assessments)

Serum (and plasma) samples for pharmacodynamic assessments will be drawn according to the schedule presented in the SOA (Table 7).

Pharmacodynamic assessments will include monitoring levels of key analytes in the serum over time. Key analytes include, but are not limited to, the following:

- Homeostatic/proliferative cytokines: IL-2, IL-7, and IL-15
- Inflammatory and immune modulating cytokines: interferon gamma (IFN-γ), IL-1, IL-6, IL-13, IL-17, IL-1 receptor antagonist (IL-1RA), granulocyte-macrophage colony stimulating factor (GM-CSF), TNF-α, and IL-12p40/p70
- Immune effector molecules: granzyme A, granzyme B, perforin
- Correlates of the acute phase response proteins: CRP, serum amyloid A (SAA), soluble IL-2
- receptor alpha (sIL-2Rα), and ferritin
- Chemokines: IL-8, C-X-C motif chemokine ligand-10 (CXCL-10), and monocyte chemotactic protein-1 (MCP-1).

5.28. Other Exploratory Assessments

Cerebrospinal fluid (CSF) may be harvested from subjects who develop neurological events or CRS to enable evaluation of inflammatory cytokines and chemokine levels. As applicable, lymphocyte or myeloid populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

Blood (PBMCs), product, tumor biopsies, bone marrow samples and CSF samples will be used for additional exploratory analyses, including lymphocyte subsets, tumor microenvironment characteristics and prognostic disease markers. Analyses may be performed by flow cytometry,

qPCR, and/or gene expression profiling. The remaining samples may be stored for future exploratory analyses related to the treatment or disease under study and might include immune or disease-related profiling of genetic alterations, cell clonality tracing, RNA, or protein expression signatures.(Table 7 and Table 8).

5.29. Subjects With Unexplained Cytopenias or Suspicion of Hemophagocytic Lymphohistiocytosis

A bone marrow aspirate and biopsy should be considered for any subject with unexplained cytopenias or where there is suspicion of hemophagocytic lymphohistiocytosis (HLH). The samples will be reviewed at the local laboratory, and a portion of the sample will also be sent to the central laboratory for exploratory analyses.

5.30. Sample Storage

Subject biospecimens, as well as any derivatives from these samples, may be stored for 15 years from the date that the last subject was treated with axicabtagene ciloleucel to address exploratory research questions related to the mechanism of action of the treatment or disease-related features. Each subject will have the right to have their sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor. The investigator should provide the sponsor the study and subject ID number so that the sample can be located and destroyed upon request in writing. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

6. STUDY TREATMENT

6.1. Description of Study Treatment

6.1.1. Description of Axicabtagene ciloleucel

Axicabtagene ciloleucel is an autologous CAR T-cell therapy that is manufactured from a subject's own T cells. The subject's T cells are collected by leukapheresis and genetically engineered ex vivo to express a CAR specific for the CD19 target antigen.

Each subject's leukapheresed cells will be shipped to the cell processing facility (CPF) where the cells are processed to enrich for the T-cell-containing PBMC fraction. Selected cells are then activated and transduced with a retroviral vector to introduce the CAR gene. The engineered T cells are then further expanded and cryopreserved to generate the IP axicabtagene ciloleucel per CPF standard operating procedures.

After manufacture and passing release criteria, axicabtagene ciloleucel is delivered to the hospital frozen in cryostorage bags or vials in a liquid nitrogen dry shipper, as described in the Investigational Product Manual (IPM). The bags or vials must be stored in vapor phase of liquid nitrogen, and the product must remain frozen until the subject is ready for treatment. Upon receipt of axicabtagene ciloleucel at the study site, verification that the product and subject-specific labels match the subject's information (subject identification [ID] number) is essential.

Refer to the IPM for details about shipping of the leukapheresis material to the CPF, manufacture of axicabtagene ciloleucel, and delivery of the product to the study site.

In exceptional cases, an axicabtagene ciloleucel product lot that does not meet certain release specification criteria may be administered to a subject, when necessary to avoid an immediate significant hazard to the subject and having considered alternative options including the product lot remanufacture. Relevant country regulations will be followed and notifications to concerned regulatory agencies and IRBs/IECs will be performed as necessary per local requirements, in case such out of specification product lot is supplied and administered to a subject.

6.2. Packaging, Labeling, Storage, and Handling of Study Treatment

6.2.1. Axicabtagene Ciloleucel Packaging, Labeling, Storage, and Handling

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is clear to opaque in clarity and white to red in color with no visible foreign particles. The cryostorage bag containing axicabtagene ciloleucel arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in vapor phase of liquid nitrogen, and the product must remain frozen until the subject is ready for treatment to assure viable live autologous cells are administered. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

Axicabtagene ciloleucel is a subject-specific product, and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject. The volume of axicabtagene ciloleucel infused, the thaw start/stop time, and axicabtagene ciloleucel administration start/stop time will all be noted in the subject medical record. Axicabtagene ciloleucel must not be thawed until the subject is ready for the infusion. Refer to the IPM for details and instruction on storage, thawing, and administration of axicabtagene ciloleucel.

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 or any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject identification labels) are identified, research staff should report the problem per the instructions in the IPM.

Refer to the IPM for details about axicabtagene ciloleucel formulation, packaging and labeling, instructions for storage and handling of axicabtagene ciloleucel, and ordering of clinical supplies.

6.3. Dosage and Administration

Axicabtagene ciloleucel treatment will consist of a single infusion of CAR-transduced autologous T cells administered intravenously on Day 0 at a target dose of 2 X 10^6 cells/kg IV.

Refer to Section 11.2 for assessments and procedures to be performed on the day of axicabtagene ciloleucel administration. Refer to the IPM for details and instructions on administration of axicabtagene ciloleucel.

Administration or dosing errors (eg, whether the complete volume in the bag was administered to the subject) should be documented in the subject's source documentation and respective eCRF.

6.4. Prior and Concomitant Medications

During the course of the study, investigators may prescribe any concomitant medications deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis except those medications listed in Section 6.5. Concomitant therapy does not include therapy used for the treatment of the disease.

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, lymphodepleting (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.

For subjects who receive the dose of axicabtagene ciloleucel, all concomitant therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent up to the Month 3 visit, and targeted concomitant therapies from this visit until 5 years after the axicabtagene ciloleucel infusion, or until a change in lymphoma therapy, or disease progression, whichever occurs first. Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations. Refer to Section 6.6 for details surrounding subsequent cancer therapy.

Specific concomitant medication collection requirements and instructions are included in the Case Report Form (CRF) completion guidelines.

6.5. Excluded Medications

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 before leukapheresis and 5 days before axicabtagene ciloleucel administration. Dexamethasone on Day 0, Day 1, and Day 2 is allowed per the study.

Systemic corticosteroids must also be avoided as a premedication in subjects for whom computed tomography (CT) scans with contrast are contraindicated (eg, subjects with contrast allergy or impaired renal clearance) if the administration is within 7 days before leukapheresis or 5 days before axicabtagene ciloleucel administration (washout period). Such subjects should undergo magnetic resonance imaging (MRI) scans with contrast or noncontrast CT scans instead during the washout period specified above. In such cases, alternative dyes such as gadolinium could be considered at the investigator's discretion.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration unless used to manage axicabtagene ciloleucel-related toxicities or discussed with the Kite medical monitor. 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.

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

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

Treatments for underlying disease, such as chemotherapy, immunotherapy, targeted agents, radiation, 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 administration.

If permissibility of a specific medication/treatment is in question, contact the Kite medical monitor. Please refer to the IB for additional information about excluded medications.

6.6. Subsequent Therapy

Subsequent therapy administered after axicabtagene ciloleucel necessary to treat a subject's disease, such as non-study-specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, will be recorded for all subjects enrolled until one of the following happens: the subject completes the long-term follow-up period, is considered lost to follow up, withdraws consent, or dies. If a subject progresses, sites are strongly encouraged to collect a biopsy confirming disease progression and to submit the biopsied tissue to the central laboratory. Treatment with axicabtagene ciloleucel is intended to be definitive therapy and not a bridge to ASCT.

6.7. Electronic Wearable Devices

An electronic wearable device will be available in this study. The device will involve a continuous temperature monitoring patch. The device can be worn up to 4 weeks per the investigator's discretion upon consent. In the event the subject is admitted to inpatient hospital setting, the device may be removed. Details on the device will be provided separately in the Electronic Wearable Device Manual. The data collected will be used for research purposes only.

6.8. Accountability and Return of Study Treatment

6.8.1. Accountability of Study Treatment

Refer to the IPM for details about accountability of axicabtagene ciloleucel.

6.8.2. Return or Disposal of Study Treatment

Unused study drug should remain in storage (at ≤ –150° C) until further instruction from Kite to either return the study drug or dispose of the study drug on site. Kite must approve the disposal of unused study drug bags on site. Refer to the IPM for details.

For return or disposal of additional study treatment products, including a comparator or products used in combination with axicabtagene ciloleucel, refer to the IPM for details.

The study monitor will review the study treatment records at periodic intervals.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of AEs and SAEs

7.1.1. AEs

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 include 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, descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches or increased blood pressure in a subject with pre-existing hypertension) must be provided.

An AE does not include the following:

- 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 study-mandated procedures, or as a precautionary measure per institutional policy are not considered AEs (refer also to Section 7.4).

- The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods is not considered to be an AE. Worsening of signs and symptoms of the malignancy under study are considered to be AEs.

7.1.2. SAEs

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

- Is fatal

- Is life-threatening (ie, an event that places the subject at immediate risk of death; it does not refer to an event that hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or prolongation of planned hospitalization (refer to Section 7.4 for definition of prolongation of planned hospitalization for this study)
  - An AE would meet the criterion of "requires hospitalization" if the event necessitated admission to a healthcare facility
  - 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 planned hospitalization
  - Refer to Section 7.4 for hospitalizations that are not considered to be SAEs.
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is another medically important serious event. 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 the NCI CTCAE; 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 in the eCRF.

Progression of the malignancy during the study is not considered to be an SAE; signs and symptoms of disease progression can be considered to be SAEs (and documented as being due to disease progression).

Refer to Section 7.5.1.2 for information and instructions for recording and reporting SAEs. Refer to Section 7.5.3 for information and instructions for recording and reporting SAEs due to disease progression.

7.1.3. Targeted AEs and SAEs

Targeted AEs /SAEs include neurologic events, hematologic events, infections, graft-versus-host disease (GVHD) or aggravation of GVHD, autoimmune disorders, and secondary malignancies.

Although only secondary malignancies are considered to be targeted AEs/SAEs, all new malignancies will be reported. All new malignancies should be reported as SAEs. New malignancies are defined as the development of any new malignancies occurring after the axicabtagene ciloleucel infusion. A secondary malignancy is defined as a new malignancy suspected to be possibly related to axicabtagene ciloleucel (ie, plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

Refer to Sections 7.5.1.1 and 7.5.1.2 for information and instructions for recording and reporting targeted AEs and targeted SAEs, respectively.

7.2. Clinical Laboratory and Vital Sign Abnormalities

7.2.1. Abnormal Clinical 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 an 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

7.2.2. 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:

- Is accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Is 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 blood pressure), only the diagnosis (ie, hypertension) should be recorded in the eCRF.

7.3. Assessments of AE and SAE Severity and Causality

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

7.3.1. Assessment of AE/SAE Severity

The severity of AEs will be graded according to the NCI CTCAE version (v) 5.0. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). For events that are not listed in the CTCAE (eg, hypogammaglobulinemia), the investigator may grade the severity according to the guidance in Table 4.

Table 4. Severity Grading of AEs

Grade	Clinical Description of Severity
1	Mild; or Asymptomatic or mild symptoms; or Clinical or diagnostic observations only; or Intervention not indicated
2	Moderate; or Minimal, local, or noninvasive intervention indicated; or Limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life-threatening; or Hospitalization or prolongation of hospitalization indicated; or Disabling; or Limiting self-care ADL[b]
4	Life-threatening consequences; or Urgent intervention indicated
5	Death related to AE

Abbreviations: ADL, activities of daily living; AE, adverse event.
a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.3.1.1. Grading of CRS and Neurologic Events

CRS is induced by activated T cells upon engagement with the CD19 antigen target. The severity of CRS events will be graded according to a modification (ie, exclusion of neurologic symptoms from the categorization of the CRS) of the grading system proposed by Lee and colleagues {Lee 2014}.

The severity of neurologic events will be graded according to the NCI CTCAE grading system. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov).

The severity of individual signs/symptoms of CRS will be graded according to the NCI CTCAE v5.0 for those signs/symptoms that are not part of the grading scale.

7.3.2. Assessment of AE/SAE Relationship to axicabtagene ciloleucel and Study Procedures

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) axicabtagene ciloleucel, 2) leukapheresis, 3) bridging therapy, 4) lymphodepleting chemotherapy, or 5) any study-specific procedure. The relationship is indicated by a "related" or "not related" response and entered in the eCRF. In assessing causality, the investigator or qualified subinvestigator will use clinical judgment and the following considerations:

- Not related: Evidence exists that the AE has an etiology other than the IP or study procedure. For SAEs, an alternative causality must be provided (eg, disease progression, concurrent disease[s], concomitant medications, or other).
- Related: There is reasonable possibility that the event may have been caused by the IP or as a result of a study procedure.

7.4. Hospitalization

Any AE that results in an unplanned hospitalization or an unplanned extension of a previously planned hospitalization should be documented and reported as an SAE as described in Section 7.5.1.1, with the following exceptions:

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for palliative or hospice care
- Hospitalization proposed by the protocol (eg, lower grade AEs that lead to admission for closer monitoring of the subject for general safety concerns, or to perform an efficacy measurement for the study).
- Planned hospitalization for a pre-existing condition
- Hospitalization due to progression of the underlying malignancy. (Refer to Section 7.5.3 for instructions on reporting underlying signs/symptoms of the underlying malignancy/disease progression as AEs/SAEs.)

7.5. Investigator Requirements and Instructions for Reporting AEs, SAEs, and Deaths to the Sponsor

7.5.1. Reporting AEs and SAEs

The investigator or a delegated and qualified subinvestigator must address the below for AEs/SAEs:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity (Section 7.3.1)

- Assessment of relatedness to axicabtagene ciloleucel, bridging therapy, leukapheresis, lymphodepleting chemotherapy, or study procedures (Section 7.3.2)

- Action taken

Additional relevant data with respect to describing the AE/SAE will be collected in the eCRFs. For AEs/SAEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the eCRF AE form. The exception is for CRS where both the diagnosis and significant signs and symptoms will be captured on the eCRF AE form.

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

Refer to Section 7.5.3 for instructions on reporting AEs/SAEs associated with disease progression.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE/SAE. In the event a subject requests to withdraw from protocol-required therapies, study-specific procedures, or the study due to an AE/SAE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA (Table 7).

Refer to Section 7.5.1.1 and Section 7.5.1.2 for additional information on reporting AEs and SAEs, respectively.

7.5.1.1. Reporting AEs

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject during the AE-reporting period described in Table 5. Refer to Section 7.5.3 for instructions on reporting AEs associated with disease progression.

Table 5. Reporting Requirements for AEs

Subjects Who Are Enrolled:	
but Did Not Receive the axicabtagene ciloleucel Infusion	**and Received the axicabtagene ciloleucel Infusion**
AEs that occur from enrollment (ie, commencement of leukapheresis) through 30 days after the last study-specific procedure (eg, leukapheresis, bridging chemotherapy, or lymphodepleting chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be reported	AEs that occur from enrollment (ie, commencement of leukapheresis) through 90 days after the axicabtagene ciloleucel infusion are to be monitored and reported
	• After 90 days, only targeted AEs will be reported until disease progression, the start of subsequent anticancer therapy, completion of the study or transition to LTFU study whichever occurs first, and will be recorded in the eCRF

Subjects Who Are Enrolled:	
but Did Not Receive the axicabtagene ciloleucel Infusion	**and Received the axicabtagene ciloleucel Infusion**
	• Targeted AEs include neurological events, hematological events, infections, graft-versus-host disease (GVHD) or aggravation of GVHD, autoimmune disorders, and secondary malignancies[a] — (Note[a]: All new malignancies are to be reported; however, only secondary malignancies are considered to be targeted AEs) All AEs deemed related to the axicabtagene ciloleucel infusion should be recorded in the eCRF and reported regardless of the study period

Abbreviations: AE, adverse event; eCRF, electronic case report form.
a New malignancies are defined as the development of any new malignancies, occurring after the axicabtagene ciloleucel infusion. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, temporally plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

7.5.1.2. Reporting SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject during the SAE reporting periods described in Table 6. Refer to Section 7.5.3 for instructions on reporting SAEs associated with disease progression.

Table 6. Reporting Requirements for SAEs

Subjects Who Are:	
• **Screen Failures** • **Enrolled but Did Not Receive the axicabtagene ciloleucel Infusion**	• **Enrolled and Received the axicabtagene ciloleucel Infusion**
For subjects who are screen failures or enrolled but did not receive axicabtagene ciloleucel infusion: All SAEs that occur from signing of the screening ICF through 30 days after the last study-specific procedure (eg, screening procedure, leukapheresis, bridging therapy, or lymphodepleting chemotherapy) or until initiation of a new anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported.	All SAEs that occur from signing of the screening ICF through 90 days after the axicabtagene ciloleucel infusion or until initiation of another anticancer therapy, whichever occurs first, will be recorded in the eCRF and reported. Refer to Section 7.5.3 for reporting deaths.
	After 90 days, only targeted SAEs will be reported until disease progression, the start of subsequent anticancer therapy, completion of the study or transition to LTFU study, whichever occurs first, and will be recorded in the eCRF. • Targeted SAEs include neurologic events, hematological events, infections, autoimmune disorders, and secondary malignancies[a] — Note[a]: All new malignancies are to be reported; however, only secondary malignancies are considered to be targeted SAEs)

Subjects Who Are:	
• **Screen Failures** • **Enrolled but Did Not Receive the axicabtagene ciloleucel Infusion**	• **Enrolled and Received the axicabtagene ciloleucel Infusion**
	After 90 days, targeted SAEs of secondary malignancies[a] will continue to be reported until subject completes the study or transition to LTFU and will be recorded in the eCRF. — All SAEs deemed related to the axicabtagene ciloleucel infusion should be recorded in the eCRF and reported regardless of study period.
	All deaths that occur from signing of the screening ICF. Refer to Section 7.5.2 and Section 7.5.3 for instructions on reporting deaths.

Abbreviations: eCRF, electronic case report form; ICF, Informed Consent Form; SAE, serious adverse event.
a. New malignancies are defined as the development of any new malignancies after the axicabtagene ciloleucel infusion; the investigator must assess causality against axicabtagene ciloleucel, lymphodepleting chemotherapy, bridging therapy, or study procedures. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, temporally plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

Unless otherwise indicated in Table 6:

- The following must be submitted to Kite via the electronic SAE (eSAE) system within 24 hours after the investigator's knowledge of the event:
  - — All SAEs
  - — CRS events Grade 3 or higher
  - — Neurologic events Grade 3 or higher
  - — All events of cerebral edema
  - — All events of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome

If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the paper SAE Report Form and sent via email to the SAE reporting mailbox: safety_FC@gilead.com. Subsequently, SAEs will be entered into the eSAE system once it becomes available.

All SAEs will be reported to the health authorities and IRB/EC per local reporting guidelines.

7.5.2. Reporting Deaths

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment. Refer to Section 7.5.3 for instructions on reporting deaths associated with the underlying malignancy/disease progression.

Any death occurring after signing of the main study ICF and within 90 days after axicabtagene ciloleucel infusion, regardless of attribution to treatment, requires expedited reporting within 24 hours after the investigator's knowledge of the event. Any death occurring after the 90 days SAE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment, the axicabtagene ciloleucel infusion, and/or study-required treatments (eg, lymphodepleting chemotherapy).

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 eCRF AE form with entries including the start date of the event and death date as the stop date of the event. Every effort should be made to capture the established cause of death, which may become available later (eg, after autopsy).

7.5.3. Reporting AEs, SAEs, and Deaths Associated With Disease Progression

Progression of the malignancy ("disease progression") as assessed by the measurement of malignant lesions on radiographs or other methods during the study, should not be reported as an AE or SAE.

For situations when an AE or SAE is due to the malignancy under investigation, the sign(s) and symptom(s), including worsening of sign(s) and symptom(s), of the malignancy under study should be reported as an AE/SAE in the appropriate section of the eCRF and the investigator should check the appropriate data field to indicate these signs and symptoms are due to the underlying disease/disease progression.

If the progression of malignancy has a fatal outcome within 90 days after the axicabtagene ciloleucel infusion, the event leading to death must be recorded as an SAE with CTCAE severity of Grade 5 and outcome of "fatal". Within this 90 day period, the outcome of death that is due to the underlying disease/disease progression must be reported immediately to Kite as an SAE, as follows:

- If there are no signs and symptoms of alternate underlying disease associated with the death (although the death has been determined to be due to disease progression), the death should be reported immediately to Kite as an SAE with the primary tumor type (eg, "acute myeloid leukemia") as the event term.

- If the death is due to a sign or symptom of the underlying disease/disease progression and the sign or symptom is a targeted SAE, then the SAE will be reported as the event term. The investigator should check the appropriate eCRF data field to indicate that these signs and symptoms are due to the underlying disease/disease progression.

7.6. Sponsor Reporting Requirements (Includes Reporting of SAEs and Deaths)

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Kite may be required to expedite to worldwide regulatory agencies reports of serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Kite or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs, as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Kite using reference safety information specified in the current IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.7. Toxicity Management

7.7.1. Toxicities Associated With Axicabtagene Ciloleucel Treatment

To date, the following important identified risks have been associated with axicabtagene ciloleucel treatment: serious neurologic adverse reactions including cerebral edema, CRS, neurologic events, cytopenias including aplastic anemia, infections, and hypogammaglobulinemia.

Refer to Section 7.3.1.1 for grading of CRS and neurologic events. Refer to the current version of the IB, Section 6 “Guidelines for Management of Important Risks” for details regarding these events.

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 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.

7.8. Special Situations Reports

7.8.1. Definitions of Special Situations

Special situation reports include all reports of medication error (eg, actual or potential, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy reports [Maternal Pregnancy and Partner Pregnancy]) regardless of an associated AE.

Medication error (actual or potential) is any unintentional error in the prescribing, dispensing, or preparation for administration or administration of an IP while the medication is in the control of a healthcare professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an IP by a clinical study subject.

Misuse is defined as any intentional and inappropriate use of an IP that is not in accordance with the protocol instructions or local prescribing information.

An overdose is defined as accidental or intentional administration of a quantity of an IP (eg, lymphodepleting chemotherapy or other study-specified IP) given per administration or cumulatively that is above the maximum recommended dose as per the protocol or product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an IP as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Kite IP.

Counterfeit or falsified medicine is defined as any IP with a false representation of 1) its identity, 2) its source, or 3) its history.

7.8.2. Instructions for Reporting Special Situations

7.8.2.1. Instructions for Reporting Pregnancies

Any pregnancy in a female subject enrolled in the study must be reported, regardless of the time after the axicabtagene ciloleucel infusion. If pregnancy occurs in a female partner of a male subject within 6 months after completing lymphodepleting chemotherapy or the axicabtagene ciloleucel infusion, whichever is longer, the pregnancy must be reported. All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or the outcome will be requested by Kite. Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

The pregnancy itself or an induced elective abortion to terminate a pregnancy without medical reasons are not considered AEs. Any premature termination of a pregnancy (eg, spontaneous abortion, induced therapeutic abortion due to complications, or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

The pregnant subject or subject partner should receive appropriate monitoring and care until conclusion of the pregnancy. The outcome should be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

If a lactation case occurs in a female subject in the study, the lactation case must be reported to Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator's awareness of the event using the Special Situations Reporting Form. In addition to reporting a lactation case during the study, investigators should monitor for pregnancy and lactation cases throughout the LTFU period. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance via email: Safety_FC@gilead.com or fax: +1 (650) 522-5477.

7.8.2.2. Reporting Other Special Situations

All other special situations must be reported on the Special Situations Reporting Form and forwarded to the Kite Patient Safety and Pharmacovigilance within 24 hours after the investigator becomes aware of the situation. These reports must consist of situations that involve study drug and/or Kite concomitant medications but do not apply to non-Kite concomitant medications.

Special situations involving non-Kite concomitant medications do not need to be reported on the Special Situations Reporting Form; however, special situations that result in AEs due to a non-Kite concomitant medication must be reported as an AE.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE Report Form. Details of the symptoms and signs, clinical management, and outcome of the AEs or SAEs will be reported, when available. Refer to Section 7.5 and the eCRF completion guidelines for instructions on special situation reporting.

7.9. Safety Review Team

An SRT will review the available composite safety after the first 6 subjects have been dosed and had the opportunity to be followed for at least 14 days to analyze risk versus benefit. Enrollment will be paused when the sixth subject is dosed and resumed after this safety evaluation as detailed in the SRT charter. If no unacceptable risk is identified, enrollment will be resumed and the study will continue with continuous real-time monitoring of safety outcomes. In order to evaluate the feasibility of the outpatient approach and to inform the Sponsor’s decision on whether to continue the study, an analysis of safety will be also performed when approximately 20 enrolled and treated subjects have been followed for at least 14 days after axicabtagene ciloleucel infusion. Enrollment will be paused when the twentieth subject is dosed and resumed after this safety evaluation as detailed in the SRT charter. Please also see Section 8.6.1.

The SRT recommendations will be formally communicated to the participating study sites.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical Analysis Plan

An overview of the SAP is provided below. Details will be provided in the SAP at finalization.

The primary objective of the study is to evaluate the safety of axicabtagene ciloleucel regimens in the outpatient setting and with the prophylaxis use of corticosteroids, as measured by the incidence and severity of CRS and neurologic events. The secondary objectives will include assessing safety and efficacy of axicabtagene ciloleucel, as measured by time to onset and duration of CRS and NE, time to hospitalization and ICU, duration of hospitalization and ICU, incidence and severity of AE of interests, ORR, CR, DOR, EFS, PFS, and OS.

8.2. Hypothesis

No formal hypothesis will be tested. All analyses will be descriptive.

8.3. Definition of Study Endpoints

8.3.1. Definition of Primary Endpoints

CRS: CRS as a syndrome (ie, a collection of individual symptoms) is identified via collection of the syndrome on a case report form specifically designed to collect CRS. Individual symptoms of CRS are separately collected on the AE log and are linked to the CRS syndrome. CRS syndrome severity is graded according to a modification of the grading system proposed by Lee {Lee 2014}. In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome; rather, they are reported on the AE log form separately based on specific symptoms per CTCAE.

Neurologic Events: Neurological AEs are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. The search strategy focuses on central nervous system toxicity, without regard to temporal relationship and concomitant conditions (eg, CRS). Additionally, the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs. Neurologic toxicity will be reported separately from CRS.

CRS rate and neurologic event rate are defined as subject incidence of CRS and NE in the safety analysis set, respectively. The worst severity grade of CRS and NE will be used to summarize the rate of CRS and NE by severity.

8.3.2. Definition of Secondary Endpoints

ORR, defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014} as determined by the study investigators. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

CR rate is defined as the incidence of an investigator-assessed complete response.

Duration of response (DOR): Among subjects who experience an objective response, DOR is defined as the date of their first objective response to disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014} or death from any cause. Subjects not meeting the criteria for disease progression and alive by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing.

EFS: EFS is defined as the time from infusion to the earliest date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014} commencement of new anti-lymphoma therapy, or death from any cause. Subjects not meeting the criteria for progression, not receiving any subsequent anti-cancer therapy and alive by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

Progression-free Survival (PFS): PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014} or death from any cause. Subjects not meeting the criteria for progression and alive by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

OS: OS is defined as the time from axicabtagene ciloleucel infusion to the date of death.

Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

8.3.3. Definition of Other Endpoints of Interest

Adverse events of interest: AEs of interest for axicabtagene ciloleucel treatment include AEs in the categories of:

Important identified risks other than CRS and neurological events:

- Cytopenias
- Infections
- hypogammaglobulinemia

Important potential risks:

- Secondary malignancies
- Replication competent retrovirus
- Tumor lysis syndrome
- Aggravation of Graft-Versus-Host-Disease

Other AESIs:

- Cardiac failure
- Cardiac arrhythmias
- Autoimmune disorders
- Bone marrow failure

Please refer to the IB for additional details on adverse events of interest.

Time to Onset of Event/Syndrome: Time to onset of an event/syndrome is defined as the time from infusion date to the day of the first occurrence of the event/syndrome.

Duration of Event/Syndrome: The duration across all events is (the end day of the last qualifying event – onset date of the first qualifying event +1), regardless of whenever the events are consecutive, overlapping, or neither. Durations of events will not be calculated for events that are ongoing at the time of the data cutoff date or subject death.

8.4. Determination of Sample Size

This study uses an open-label, single-arm design, with a planned sample size of approximately 30 subjects.

8.5. Access to Individual Subject Treatment Assignments and Minimization of Bias

This is a single-arm, open-label study, and subjects and investigators will be aware of the 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 SAP and/or SRT charter.

8.6. Planned Analyses

8.6.1. Safety Review and Early Stopping Guidelines

An SRT will review the available composite safety after the first 6 subjects have been dosed and have had the opportunity to be followed for 14 days to analyze risk versus benefit. Enrollment will be paused when the sixth subject is dosed and resumed after this safety evaluation as detailed in the SRT charter. Available PK/PD and efficacy outcomes will also be reviewed. If no unacceptable safety risk due to outpatient dosing is identified, the enrollment will be resumed, and the study will continue with continuous real-time monitoring of safety outcomes.

In order to evaluate the feasibility of the outpatient approach and to inform the Sponsor's decision on whether to continue the study, the SRT will also perform a review when approximately 20 enrolled and treated subjects have been followed for at least 14 days after axicabtagene ciloleucel infusion. Enrollment will be paused when the 20th subject is dosed and resumed after this safety evaluation as detailed in the SRT charter.

Safety data will be under continuous monitoring.

8.6.2. Primary Analysis

The primary analysis will be conducted when all enrolled and treated subjects have had the opportunity to be followed for 6 months after the infusion.

8.6.3. Final Analysis

The final analysis will occur when all enrolled subjects have withdrawn from study, lost to follow up, died or rolled over to the LTFU study.

8.6.4. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the axicabtagene ciloleucel infusion; LTFU will be performed on subjects after transition to the LTFU study (refer to Section 3.7).

After the primary analysis for this study, additional follow-up analyses of efficacy and safety will be performed as needed to satisfy regulatory requirements and perform long-term efficacy, safety, and OS follow-up.

8.6.5. Analysis Conventions

8.6.5.1. Analysis Sets

The following analysis sets will be used to analyze study data:

- Full analysis set: Consists of all enrolled subjects. The full analysis set will be used for summaries of subject disposition.
- Safety analysis set: Consists of all subjects treated with any dose of axicabtagene ciloleucel
- Efficacy evaluable set: Efficacy endpoints will be based on efficacy evaluable set consisting of all subjects enrolled and treated with axicabtagene ciloleucel at a target dose of 2 $x10^6$ anti-CD19 CAR T cells/kg and who have documented disease at baseline and subsequent tumor assessment following axicabtagene ciloleucel infusion. The efficacy evaluable set will be used for all efficacy analyses unless otherwise specified.

8.6.5.2. Data Handling Convention

Every effort will be made to obtain complete data for all important endpoints. In the case of missing data, missing values will be imputed or censored using appropriate statistical approaches with sensitivity analysis. More detail will be provided in the SAP.

8.7. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods. More detail will be provided in the SAP.

8.8. Efficacy Analysis

8.8.1. Objective Response Rate

The incidence of objective response and exact 2-sided 95% CIs will be generated for efficacy evaluable set subjects.

8.8.2. Best Objective Response

The incidence of subjects with CR, PR, SD, PD, and not evaluable (as the best response to treatment) and exact 2-sided 95% CIs about the incidence will be generated for efficacy evaluable set subjects.

8.8.3. EFS, DOR, PFS and OS

Kaplan-Meier (KM) estimates and 2-sided 95% CIs will be generated for EFS, DOR, PFS, and OS for efficacy evaluable subjects. The median time and event-free rates at 3-month intervals will be provided.

8.9. Safety Analysis

Subject incidence rates of treatment-emergent AEs (TEAEs), defined as AEs with an onset on or after the axicabtagene ciloleucel infusion, will be summarized. TEAEs including all, serious, fatal, CTCAE v5.0 Grade 3 or higher, and treatment-related AEs will be tabulated by preferred term and/or system organ class. CTCAE grade worsening in selected safety laboratory values will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized. Clinical and laboratory AEs will be coded using MedDRA.

Tables and/or narratives of deaths through the post-treatment follow-up will be provided. More details of safety analysis can be found in the SAP.

8.10. Other Analysis

At various timepoints throughout the study, ad hoc data analyses may be conducted to review the ongoing safety and efficacy outcomes.

8.11. Multiplicity Adjustment

No multiplicity adjustment is needed, given no hypothesis is to be tested.

8.12. Pharmacokinetics Analysis

The peak, AUC (from Day 0 to Day 28), and time to peak for anti-CD19 CAR T cells will be summarized.

8.13. Pharmacodynamics Analysis

The peak, AUC (from Baseline to Day 28), and time to peak will be tabulated for analytes (pro-inflammatory and immune-modulating cytokines, chemokines, and effector molecules) in serum/plasma over time.

8.14. Patient-reported Outcome Analysis

Changes in EQ-5D-5L index and VAS scores from baseline will be summarized at each post-treatment study visit with descriptive statistics. In addition, the mean/median changes in EQ-5D-5L index and VAS scores from baseline over time will be presented.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the IP during the course of a clinical study. This documentation must be provided before the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Kite of any change in reportable interests during the study and for 1 year after completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. IRB/IEC Approvals

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each study 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 are to submit site-specific and study SAEs (provided to the study site by the key sponsor contact) along with any protocol deviations to their IRB/IEC in accordance with their respective IRB/IEC policies.

9.1.3. Informed Consent

Before a subject can participate in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and potential risks. The consent process and subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the most current IRB/IEC-approved ICF is to be signed and personally dated by the subject and person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with the institution's 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 relevant to their participation in the study.

In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to allow the use of the remainder of their already collected specimens for optional future research, which might include genetic testing (eg, characterization of DNA and RNA mutations/ sequences), in accordance with applicable regulations. The results of the tests done on the samples will not be given to the subject or investigator.

9.1.4. Confidentiality

The investigator must assure that the subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an ID code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Kite or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded for the proper subject (refer to specific laboratory instructions for further information). Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Kite, including but not limited to the IB, this protocol, eCRFs, the study drug, and any other study information, remain the sole and exclusive property of Kite during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Kite. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Per federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/GCP guidelines, investigators and institutions are required to permit direct access to the sponsor, CRO, 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 include personal information.

Subject confidentiality must be maintained on all material 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 to local laws and regulations

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

9.1.5. Study Files and Retention of Records

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfill 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. Example of such source documents may include, but are not limited to, hospital records and patient charts, laboratory, pharmacy, radiology and records, subject diaries, microfiches, correspondence, and death registries.

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

- Subject content including ICFs and subject ID lists
- Essential documents for the conduct of this clinical study
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence.

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

The required source data should include sequential notes containing at least the following information for each subject:

- Subject ID
- Documentation that the subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis [to support inclusion and exclusion criteria])
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in the study (including study number/name)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed

- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of the IP, including the start and stop times of the axicabtagene ciloleucel infusion
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medications (including the start and end dates, dose [if relevant], and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

Traceability records for the product, from procurement through manufacture to administration of the product, should be kept by each relevant party (eg, the sponsor and investigator/institution) for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by agreement with Kite. Before, during, and after completion or termination of the trial, each party should hold the necessary information available at all times to ensure bidirectional traceability, linking the subject information at the procurement site to the product and subject information at the study site to the product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kite to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

If a subject transfers to another study site, the investigator must notify Kite in advance before assigning the subject's study records to another party or moving them to another location.

9.1.6. Electronic Case Report Forms

All data will be collected in an eCRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of eCRFs, refer to the eCRF completion guidelines.

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol SOA and procedures. The eligibility criteria and enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF completion guidelines provided by the sponsor.

Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Kite staff who routinely review the data for completeness, correctness, and consistency. The study site investigator or coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry and providing the reason for the update (eg, data entry error). Original entries, as well as any changes to data fields, will be stored in the audit trail of the system. At a minimum, before any interim time points or database lock (as instructed by Kite), the investigator will use his/her log-in credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents.

At the conclusion of the study, Kite will provide the study site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Access to Study Information

The investigator will make available all source documents and other records for this study to Kite's appointed study monitors, IRBs/IECs, or regulatory or health authority inspectors. By signing the investigator statement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits, audits, and regulatory authority inspections.

9.1.8. Protocol Compliance

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Kite. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented approval before modifications can be implemented. Documentation acknowledging agreement with the protocol amendment from the investigator and approval from the IRB/IEC are to be submitted to the key sponsor contact.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Kite will ensure that the report meets the standards set out in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Kite in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Kite any proposed publication or presentation along with the respective scientific journal or presentation forum, at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Kite's confidential information (see Section 9.1.4).
- The investigator will comply with Kite's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold the publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.2.3. Financing and Insurance

Kite has insurance that provides compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Kite will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3. Joint investigator/Sponsor Responsibilities

9.3.1. Good Clinical Practice

The investigator, sponsor, and sponsor delegates will ensure that this study is conducted in accordance with ICH GCP guidelines, including the E6(R2) addendum for GCP, and applicable laws and regulations.

9.3.2. Quality Control and Quality Assurance

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 to assure that subject confidentiality is respected.

The monitor is responsible for source document verification of eCRF 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.

In accordance with ICH GCP and the audit plan, a study site may be chosen for a Kite Quality Assurance site audit. A Kite Quality Assurance 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. investigators will provide Kite Quality Assurance auditors access to subject records.

Representatives of regulatory authorities may conduct inspections of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.3. Ethics

Study KT-US-482-0137 (ZUMA-24) will be conducted under a US Investigational New Drug (IND) application or equivalent and in accordance with recognized international scientific and ethical standards, including but not limited to, the ICH guideline for GCP and original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US CFR Title 21, Part 312, and European Community Directive 2001/20/EC, as well as other local legislation.

9.3.4. Study Discontinuation

Both Kite 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 of the trial completion or early termination.

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11. APPENDICES

Section 11.1 Sponsor and Investigator Signature Page
Section 11.2 Schedule of Assessments
Section 11.3 Childbearing Potential and Birth Control
Section 11.4 Disease Response Criteria
Section 11.5 Patient-reported Outcomes
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Section 11.7 Protocol Amendment History

11.1. Sponsor and Investigator Signature Page

KITE PHARMA, INC.
2400 BROADWAY
SANTA MONICA, CA 90404

STUDY ACKNOWLEDGMENT

A PHASE 2 OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL CONCOMITANT WITH PROPHYLACTIC STEROIDS IN SUBJECTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA IN THE OUTPATIENT SETTING

Amendment 3.0, 05 February 2025

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

PPD
Kite Medical Monitor Name (Printed)

[Refer to the appended electronic signature]
Signature

[Refer to the appended electronic signature]
Date

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 (ICH) 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)
- Subinvestigators (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

11.2. Schedule of Assessments

A schedule of assessments (SOA) and procedures to be performed during the treatment and post-treatment follow-up periods is presented in Table 7. An SOA and procedures to be performed during the post-treatment follow-up period is presented in Table 8.

Table 7. SCHEDULE OF ASSESSMENTS: TREATMENT AND POST TREATMENT PERIODS

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy (Optional)	Conditioning Chemotherapy Period					IP and Corticosteroid Administration Period[A]			Post Treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days before enrollment/ leukapheresis	Within approx. 5 days after eligibility confirmation	Start after leuk; stop 7 days prior to cond chem	-5	-4	-3	-2	-1	0	1 - 7	10	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
Informed Consent	X														
Medical and Treatment history	X														
Physical examination	X			X	X	X			X	X		X	X	X	X
Weight (plus Height at screening)	X	X													
Vital signs (BP, HR, RR sPO_2 sat, temp)[B]	X	X		X	X	X			X	X		X	X	X	X
Wearable Device [C]				X	X	X			X	X					
ECOG Performance Status	X														
ECG	X														
ECHO or MUGA	X														
Brain MRI	X														
Lumbar Puncture[D]	X									X			X		
Bone marrow biopsy/aspirate[F]										X					
Archival and fresh tumor samples[G, E]	X									Optional: Day 5 (+/- 2 days)					
PET-Diagnostic CT/disease assessment[H]	X												X		X
EQ-5D-5L	X												X		X
Neurologic examination including a cognition assessment[I]	X								X	Daily			X		X
Local laboratory draw															
Chemistry panel (serum)	X	X		X	X	X			X	X		X	X	X	X
CBC w/differential (blood)	X	X		X	X	X			X	X		X	X	X	X

Procedures	Screening	Enrollment/ Leukapheresis	Bridging Therapy (Optional)	Conditioning Chemotherapy Period					IP and Corticosteroid Administration Period[A]			Post Treatment Follow-up (each visit calculated from Day 0)			
Day	Within 28 days before enrollment/ leukapheresis	Within approx. 5 days after eligibility confirmation	Start after leuk; stop 7 days prior to cond chem	-5	-4	-3	-2	-1	0	1 - 7	10	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 2 (± 1 week)	Month 3 (± 1 week)
LDH (serum)	X														
CRP and Ferritin (serum)		X		X					X	X					
Pregnancy test (serum or urine)	X			X											X
Serology (HIV/HepB/HepC)[J]	X	X													
Central laboratory draw															
Serum/plasma analytes[K]		X							X	Day 1, 3, 5, 7	X	X	X		
CBC w/differential (blood)		X								Day 1, 3, 7	X	X	X		X
Axicabtagene ciloleucel CAR T cells[K, L, E] exploratory analysis (PBMCs)[L]		X							X	Day 1, 3, 7	X	X	X		X
RCR analysis (PBMCs)[M]									X						X
Leukapheresis		X													
Fludarabine/ Cyclophosphamide				X	X	X									
Dexamethasone 10 mg[N]									X	Day 1, 2					
Axicabtagene ciloleucel infusion IV									X						
Adverse events/Concomitant medications	X	X	X	→											

Abbreviations: BP, blood pressure; CAR, chimeric antigen receptor; CBC, complete blood count; CNS, central nervous system; CSF, cerebrospinal fluid; CRP, C-reactive protein; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HR, heart rate; IP, investigational product; IV, intravenous; MRI, magnetic resonance imaging; PET-CT, positron emission tomography–computed tomography; QOD, every other day; RCL, replication-competent lentivirus.

A. Refer to Table 8 for monitoring after axicabtagene ciloleucel infusion
B. Vital signs should be obtained during and after axicabtagene ciloleucel infusion at the specified timepoints at the healthcare facility. During any inpatient hospitalization monitor at a minimum of every 6 hours.

C. Wearable device will be deployed on Day -5 for continuous temperature monitoring. The device can be worn up to 4 weeks per the investigator's discretion. In the event the subject is admitted to inpatient hospital setting, the device may be removed.
D. Lumbar puncture:
   - 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 CSF for possible CNS involvement.
   - Subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion will have lumbar puncture performed and sample sent to the central laboratory to assess levels of key analytes, immune cell subsets and the presence of CAR T cells in CSF, unless contraindicated.
   - Measurement of the opening pressure should be done, when possible, with recording of the results in the subject site chart.
   - Subjects who sign the optional portion of the consent will have lumbar puncture for the collection of CSF at baseline before axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion (Day 5 +/-2 days and week 4 +/- 3 days).
E. Assessments to be performed at disease progression: Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.
F. As applicable, bone marrow biopsy aspirate will be performed to confirm response and a portion will be sent to the central laboratory (ie, for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities after axicabtagene ciloleucel.
G. Archival tumor sample: Either FFPE tumor block or 20 unstained slides. Archived tumor samples should be submitted to central laboratory after eligibility has been confirmed and prior to start of lymphodepleting (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. Post treatment fresh tumor samples (if applicable) will be collected/submitted on Day 5 (±2 days).
H. PET-CT (neck-chest-abdomen-pelvis)/disease assessment: Screening PET-CT should be completed as close to enrollment as possible. If PET-CT is performed following last line of therapy, it may be used for confirmation of eligibility and to establish baseline if it was performed ≤ 28 days before enrollment. If PET-CT is performed > 28 days prior to the initiation of lymphodepleting (conditioning) chemotherapy or if subject receives any anticancer therapy between screening and lymphodepleting (conditioning) chemotherapy, baseline scans must be repeated.
I. Neurologic examination including a cognition assessment: If subject has an extended hospitalization after Day 7, a neurological exam including a cognition assessment will continue to be performed every other day.
J. Viral serologic tests (eg, HIV, hepatitis B, and hepatitis C) will be carried out per institution guidelines and US regulations. Testing may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.
K. Axicabtagene ciloleucel CAR T cells (PBMCs) and cytokines (serum/plasma):
L. If a subject is admitted to the hospital during the 7-day observation period with any axicabtagene ciloleucel -related AEs, blood samples for assessment of axicabtagene ciloleucel CAR T cells (PBMCs) and cytokines (serum/plasma) will be collected on the day of hospital admission and then weekly through, and including, the day of discharge.
M. Blood samples for assessment of axicabtagene ciloleucel CAR T cells (PBMCs) and cytokines (serum/plasma) should also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.
N. If the subject experiences a Grade 3 or higher axicabtagene ciloleucel-related toxicity, such as Grade 3 CRS or neurologic event, 1 additional blood draw for anti-CD19 CAR T cells (PBMCs) and analytes (serum/plasma) will be collected at the time of the Grade 3 or higher axicabtagene ciloleucel-related toxicity and upon resolution of the event.
O. Exploratory analyses (PBMCs): Exploratory analyses will include lymphocyte subsets.
P. RCR: collect PBMCs on Day 0 prior to administration of axicabtagene ciloleucel and at Month 3, 6, and 12; then, collected and analyzed yearly, for up to 15 years,only if positive at Month 3, 6, or 12 or if clinically suspected. If minimal cells are available from the Day 0 collection, RCR will be tested using Leukapheresis PBMCs. A separate sample collection for RCR is unnecessary if PBMCs are scheduled to be collected on the same day as per the SOA.
Q. Administered dexamethasone 10 mg po or IV daily on Day 0 (pre axicabtagene ciloleucel), Day 1 and Day 2.

Table 8. SCHEDULE OF ASSESSMENTS: LONG-TERM FOLLOW-UP PERIOD

Procedure	Long Term Follow-up Period (Note: Each visit calculated from Day 0. One month is defined as 28 days)					Relapse / Disease Progression[G]
Visit Frequency	**Month 6 (± 1 week)**	**Month 9 (± 1 week)**	**Month 12 (± 1 week)**	**Month 15 (± 1 week)**	**Month 18[F] (± 1 week)**	
Physical examination	X	X	X	X	X	X
PET-CT/disease assessment[A]	X	X	X	X	X	
EQ-5D-5L	X					
Survival status	X	X	X	X	X	
Central laboratory draw						
Tumor Biopsy (optional)[G]						X
CBC w/differential (blood)[G]	X	X	X		X	X
Axicabtagene ciloleucel CAR T cells and exploratory assessments (PBMCs)[G]	X	X	X		X	X
RCR analysis (PBMCs)[B]	X		X			
Targeted AEs/SAEs[C]	X	X	X	X	X	
Targeted concomitant medication[D]	X	X	X	X	X	
Subsequent therapy for NHL[E]	X	X	X	X	X	X

Abbreviations: AE, adverse event; CAR, chimeric antigen receptor; CBC, complete blood count; NHL, non-Hodgkin lymphoma; PET-CT, positron emission tomography-computed tomography; RCL, replication-competent lentivirus; SAE, serious adverse event.

A. PET-diagnostic CTs/disease assessments will continue through Month 18 or until disease progression, whichever comes first**.** If subject's disease has not progressed by Month 18, disease assessments will continue to be performed per standard of care.
B. RCR: PBMCs to be collected at Month 3, 6, and 12, then collect yearly, if positive for RCR, for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12, or if clinically suspected. When PBMCs are collected for assessment of axicabtagene ciloleucel CAR T cells levels, a separate PBMC collection for assessment of RCR is not required.
C. Targeted AEs/SAEs include neurologic disorders, autoimmune disorders, hematologic disorders, serious infections, and secondary malignancies will be collected for 18 months or until disease progression, whichever occurs first. Targeted AEs/SAEs considered possibly related to axicabtagene ciloleucel will be collected after 18 months up to 15 years in a LTFU study (KT-US-982-5968) or until disease progression, whichever occurs first
D. Targeted concomitant medications including gammaglobulins, immunosuppressive drugs, anti-infective drugs, and vaccinations will be collected for 18 months or until disease progression, whichever occurs first.
E. Subsequent therapy administered after axicabtagene ciloleucel infusion for a subject's disease such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy must be collected until subject completes the long-term follow-up 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.
F. Subjects who complete approximately 18 months follow up will be transitioned to a LTFU study (KT-US-982-5968). In the event the transition to LTFU study is delayed, subjects should continue to have scheduled visits every 6-month intervals until LTFU transition is completed. If the study is terminated early, all subjects who were infused with axicabtagene ciloleucel will be transitioned to the LTFU study, KT-US-982-5968, at the time of study termination.
G. Assessments to be performed at disease progression: Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur, even if this requires an unscheduled visit.

11.3. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trial Facilitation Group (CTFG) {Clinical Trials Facilitation Group (CTFG) 2014}, as described in the following sections.

11.3.1. Definition of Childbearing Potential

A female is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

11.3.2. Birth Control Methods That May Be Considered as Highly Effective

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[a]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Injectable
  - Implantable[b]

[a] Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

- Intrauterine device (IUD)[b]
- Intrauterine hormone-releasing system (IUS)[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b,c]
- Sexual abstinence[d]

11.3.3. Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM). A female condom and a male condom should not be used together.

[c] A vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] 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 preferred and usual lifestyle of the subject.

11.4. Disease Response Criteria

11.4.1. International Working Group Lugano Classification

Disease assessments are to be performed according to the International Working Group Lugano Response Criteria for Malignant Lymphoma {Cheson 2014};

The Deauville 5-point scale (5PS) is used for PET scoring; the scores and their descriptions are presented in Table 9.

Table 9. Deauville 5-point Scale for PET Scoring

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

Source: {Cheson 2014}.

11.4.1.1. Complete Remission

11.4.1.1.1. Complete Metabolic Response for PET−CT-based Response

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

- A 5PS score of 1, 2, or 3, with or without a residual mass:
  - In Waldeyer's ring or extranodal sites with high physiologic uptake or activation within the 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 FDG-avid disease in bone marrow

11.4.1.1.2. Complete Radiologic Response for CT-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 extra lymphatic 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

11.4.1.2. Partial Remission

11.4.1.2.1. Partial Metabolic Response for PET–CT-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 the interim, these findings suggest responding disease

  — At the 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 imaging or biopsy or an interval scan.

11.4.1.2.2. Partial Radiologic Response for CT-based Response

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

- ≥ 50% decrease in the 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 (CT) scan, assign 5 mm × 5 mm as the default value

  — When the lesion is no longer visible, assign 0 x 0 mm

  — For a node > 5 mm × 5 mm, but smaller than normal, use the 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

11.4.1.3. Stable Disease

11.4.1.3.1. No Metabolic Response for PET–CT-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 with baseline (screening) at an interim time point or the end of treatment
- No new sites of disease should be observed
- No change from baseline in bone marrow

11.4.1.3.2. Stable Radiologic Disease for CT-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 ofup to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease (PD) are met
- No increase consistent with progression in nonmeasured lesion and organ enlargement
- No new sites of disease should be observed

11.4.1.4. Progressive Disease

11.4.1.4.1. Progressive Metabolic Disease for PET–CT-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 nadir and/or
- New FDG-avid foci consistent with lymphoma at an interim time point or the end of treatment assessment
- New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection or inflammation). If uncertain regarding the etiology of new lesions, a biopsy or interval scan may be considered
- New or recurrent FDG-avid foci in bone marrow

11.4.1.4.2. Progressive Radiologic Disease for CT-based Response

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

- An individual node/lesion must be abnormal with:
  - LDi > 1.5 cm, and
  - An increase by ≥ 50% from the cross product of LDi and perpendicular diameter nadir, and
  - An increase in LDi or shortest transverse diameter, shortest axis perpendicular to the LDi, (shortest transverse diameter) 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 there is no prior splenomegaly, the spleen must increase by ≥ 2 cm from baseline
  - New or recurrent splenomegaly
- New or clear progression of preexisting 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 attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

11.5. Patient-reported Outcomes

11.5.1. European Quality of Life 5-dimension 5-level Questionnaire

The European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) is a generic measure of health status captured on the day of assessment. Two components comprise the EQ-5D-5L: the EQ-5D descriptive system and the EQ visual analog scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is divided into 5 levels of severity: “nor problems”, “slight problems”, “moderate problems”, “severe problems”, and “extreme problems”.

The EQ-5D-5L VAS is a vertical VAS for recording self-rated current HRQoL state reported from 0, described as “the worst health you can imagine”, to 100, described as “the best health you can imagine”.

EQ-5D-5L will be scored according to the published administration and scoring manual {EuroQol Research Foundation 2019} which can be found here: https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf.

The EQ-5D-5L takes approximately 5 minutes to complete. It is expected to be completed by the subject before any procedures are performed, excluding blood draws, and at the time points noted in the SOAs (Section 11.2).

11.6. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Subject safety monitoring and follow-up:

   a) Subjects may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

      Mitigation plan: For subjects who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a remote study visit, via phone or video conferencing, to assess the subjects within the target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

      i. Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AEs/SAEs.

      ii. Review the current list of concomitant medications and document any new concomitant medications.

      iii. If applicable, confirm electronic/paper diary questionnaires and patient-reported outcomes have been completed and transmitted.

   b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, blood draws, imaging, physical exams).

      Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow-up per protocol. Any changes in the party conducting laboratory assessments for the study because of the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible. Central lab kits may be sent to subject's local hospital lab for sample collection. Relevant imaging (eg, PET-CT, CT) can be done at the subject's local hospital and images transferred or sent to the investigative site. Physical exams can be completed by a local physician with results sent to investigative site.

   c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form version.

      Mitigation plan: The site staff will follow their approved informed consent process and remain in compliance with the local ethics committee/institutional review board and national laws and regulations. Remote consent will be allowed if has been approved by the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the investigative site at the earliest opportunity.

2) Protocol and monitoring compliance:

   a) Protocol deviations may occur in situations where scheduled visits or procedures cannot be conducted as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure at a protocol-specified time point, an unscheduled visit should be conducted as soon as possible when conditions allow so that the required procedure can be performed. The situation should be recorded and explained as a protocol deviation. Any missed subject visits must be reported in the eCRF, if possible, and recorded as deviations to the protocol because of the pandemic, so that they can be appropriately documented and described in the clinical study report. Any remote study visits that are conducted in lieu of clinic visits because of the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in source data verification, an increase in protocol deviations, or underreporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure ongoing data entry and query resolution. Remote source data verification may be arranged if allowed by local regulation and the Study Monitoring Plan. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct an off-site monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on-site, must be tracked centrally and updated on a regular basis.

3) Missing data and data integrity:

   There may be an increased amount of missing data because of subject's missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

   Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (eg, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of axicabtagene ciloleucel in study subjects remains unchanged.

11.7. Protocol Amendment History

A high-level summary of this amendment is provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

A separate tracked change (red-lined) document comparing the original protocol to this amendment will be made available upon the publication of this protocol.

11.7.1. Amendment 3.0 (05 Feb 2025)

Section Number and Name	High-level Description of Change	Brief Rationale
Throughout protocol	Subjects are eligible to transition to a separate long term follow-up study upon completion of approximately 18 months of follow-up	Executive leadership decision to reduce the duration of follow-up from 24 months to 18 months
Study Procedures 5.25 RCR	Added clarification language for RCR testing timepoints	To provide further clarification of collection requirements
7.1.3 Targeted AEs and SAEs	Added graft-versus-host disease (GVHD) or aggravation of GVHD as a targeted AE	To align protocol with updated AEs/ SAEs

11.7.2. Amendment 2.0 (29 Mar 2024)

Section Number and Name	High-level Description of Change	Brief Rationale
Protocol Title Page 11.1 Sponsor and Investigator Signature Page	Added Amendment 2.0 and date	To update the current amendment information
Protocol Synopsis 2.0 Objectives and Endpoints 5.28 Other Exploratory Assessments 8.3.3 Definition of Other Endpoints of Interest 11.2 Schedule of Assessments	Remove immunogenicity testing	To align with active Yescarta studies
Protocol Synopsis 3.1 Study Design 4.1 Number of Subjects and Subject Selection 8.4 Determination of Sample Size	Decrease subjects to be enrolled from 40 to 30	To lower the number of subjects needed to complete study
11.2 Schedule of Assessments	Remove [See Note} from schedule of events	Administrative change as there was no note to reference
Figure 1 Study schema	Administrative change	Updated time of proximity to align with amendment 1

Section Number and Name	High-level Description of Change	Brief Rationale
Protocol Synopsis 2.0 Objectives and Endpoints	Addition of 3 days to rate of hospitalization. Updated exploratory language	To align with standard for outpatient treatment To provide further clarification of exploratory objective and endpoint
7.4 Hospitalization	Added clarification language consistent with the seriousness criteria as understood by Safety	To provide site with clarity around type of hospitalization
3.1 Study Design 3.7 Long-Term Follow-up	Added clarification language consistent with transition to LTFU study	To align with active Yescarta studies
7.1.3 Targeted AEs and SAEs	Added clarification language “All new malignancies should be reported as SAEs”	To align with new protocol template/ section on reporting AEs/ SAEs
Table 5. Reporting Requirements for AEs Table 6. Reporting Requirements for SAEs 7.5.2 Reporting Deaths 7.5.3 Reporting AEs, SAEs, and Deaths Associated With Disease Progression	Updated reference of reporting period of “3 months” to “90 days” across safety section	To align with new protocol template/ section on reporting AEs/ SAEs

11.7.3. Amendment 1.0 (13 Sep 2023)

Section Number and Name	High-level Description of Change	Brief Rationale
Protocol Synopsis Key Inclusion Criteria and Key Exclusion Criteria 4.2.1 Inclusion Criteria 4.2.2 Exclusion Criteria 1.4 Study Rationale 5.4 Bridging Therapy	Inclusion criteria #2 updated to include 1 or more lines of therapy Removed Exclusion criterion “Received more than 1 line of therapy for LBCL” Removed specifics of bridging therapy	To improve enrolment by expanding eligibility To align with inclusion # 2
Protocol Synopsis 3.1 Study Design 5.3 Leukapheresis 5.6. Axicabtagene Ciloleucel	Changed travel distance to study site to 2 hours	To align with US Yescarta label
Protocol Synopsis Statistical Methods 8.10 Other Analysis	Include an adhoc analysis at any time during the study	To allow data cut/review prior to the primary analysis for possible ASH 2024 submission in case enrolment timeline is not met

Section Number and Name	High-level Description of Change	Brief Rationale
5.18 Archival and Fresh Tumor Biopsy Table 7 SCHEDULE OF ASSESSMENTS: TREATMENT AND POST TREATMENT PERIODS footnote G	Deleted language that a fresh tumor sample is required for confirmation of diagnosis.	To clarify that tissue collection for confirmation of diagnosis should be encouraged but not required.
Protocol Synopsis, Study design	Added clarification language: "following axicabtagene ciloleucel infusion"	To provide clarification regarding the exact timeframe
Protocol Synopsis 3.9 Number of Participating Study Sites	Updated the number of study sites from approximately 15 to 20	To reflect the study-wide decision to increase the number of study sites
1.3.2. Clinical Studies With Axicabtagene Ciloleucel 10. REFERENCES 1.4 Study Rationale	Include data from ZUMA-7 Moved certain language to 1.3.2	To include additional summary of available data from relevant clinical studies that potentially have clinical significance to the study
Protocol Synopsis 3.1. Study Design 3.7. Long-term Follow-up Table 8. SCHEDULE OF ASSESSMENTS: LONG-TERM FOLLOW-UP PERIOD	1) Added language throughout document to allow subjects to roll over following axicel infusion, instead of having to wait for Month 24 visit 2) Changed "may" to "will (be transitioned to.LTFU study)"	To remove the delay until Month 24 for LTFU subject roll over as needed, ie. in case the study terminates early Changed language to align with Kite Clinical Protocol template
5.15. Brain MRI/Imaging	Added contrast enhanced CT scan if contraindication to MRI	To provide an alternative option for instances when MRI is contraindicated
5.5. Lymphodepleting (Conditioning Chemotherapy)	Added language to contact the medical monitor with any reductions in LD dose	To provide guidance to sites if LD dose reduction is needed
8.3.1 Definition of Primary Endpoints	Added definition for CRS and neurological event rate	To clarify endpoints
Protocol Synopsis 5.6.3.1. Day 0 5.6.3.2. Days 1 to 7	Clarified that vital signs and neurological assessment on Days 0 to 7 while away from clinic should be done per site guidelines.	To clarify the vital signs monitoring while away from clinic during Days 0 to 7
11.6 Pandemic Risk Assessment and Mitigation Plan	New section	Kite Clinical Protocol template change from v2.0 to v3.0
11.7 Protocol Amendment History	New section – Protocol changes to be summarized in tabular form in protocol; no Summary of Changes document needed	Kite Clinical Protocol template change from v2.0 to v3.0

Section Number and Name	High-level Description of Change	Brief Rationale
5.19 Positron Emission Tomography-diagnostic CT Scans 11.4.1 International Working Group Lugano Classification	Remove language referring to the "study imaging manual"	There is no central imaging on this study; therefore, this language is not applicable.
5.25. RCR Table 2. Clinical Laboratory Tests for Safety Assessments Table 7. SCHEDULE OF ASSESSMENTS: TREATMENT AND POST TREATMENT PERIODS Table 8. SCHEDULE OF ASSESSMENTS: LONG-TERM FOLLOW-UP PERIOD	Added language regarding PBMC collection requirements and timing	To clarify that PBMCs should only be collected and analyzed if RCR was positive at any time point in the first 12 months (Month 3, 6, or 12) or if RCR is clinically suspected.
11.5.1. European Quality of Life 5-dimension 5-level Questionnaire	Added template language and deleted the copy of survey sample	Kite Clinical Protocol template change from v2.0 to v3.0
Table 2. Clinical Laboratory Tests for Safety Assessments	1) Deleted "screening only" on creatinine clearance requirement 2) Clarified language around Cockcroft Gault formula usage	3) To allow creatinine clearance monitoring to beyond the Screening visit ie. for continued renal function monitoring of subjects with compromised organ function 4) To acknowledge variations in CrCl calculation methods across sites
Table 6. Reporting Requirements for SAEs	1) Removed repetitive language and added that investigator must assess causality 2) Deleted "pregnancy or lactation exposure" from the list of submissions to Kite via the electronic SAE (eSAE) system	1) To provide further clarification on targeted AE reporting 2) "Pregnancy or lactation exposure" is only reported via paper. Applicable instructions are outlined in *Section 7.8.2.1.*
Cover page 2 1.6 Compliance	Moved compliance text to front of document	Administrative update
Table 7. SCHEDULE OF ASSESSMENTS: TREATMENT AND POST TREATMENT PERIODS 5.5. Lymphodepleting (Conditioning Chemotherapy) 5.6.3.1. Day 0	Wearable device start updated from Day 0 to Day -5	To allow time to troubleshoot issues before data collection starts on Day 0
Table 8. SCHEDULE OF ASSESSMENTS: LONG-TERM FOLLOW-UP PERIOD	Added visit windows and defined a month as equivalent to 28 days	To provide clarification regarding visit windows during the LTFU period

KT-US-482-0137 (ZUMA-24) Protocol Amendment 3.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	13-Feb-2025 18:51:01