CLINICAL STUDY PROTOCOL

A PHASE 2 MULTICENTER STUDY OF AXICABTAGENE CILOLEUCEL IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA (INHL)

Protocol Number:	KTE-C19-105 (ZUMA-5)
USAN/INN:	Axicabtagene ciloleucel
Company Code:	KTE-C19
IND Number:	016278
ClinicalTrials.gov Identifier	NCT03105336
EU CT Number:	2023-505169-10-00
Clinical Study Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
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Original Protocol Date: **Protocol Amendment #1:** **Protocol Amendment #2:** **Protocol Amendment #3:** **Protocol Amendment #4:** **Protocol Amendment #5:** **Protocol Amendment #6:** **Protocol Amendment #7:**	26 Nov 2016 29 Aug 2017 19 Jan 2018 07 Sep 2018 29 Nov 2018 24 Jul 2019 08 Jul 2020 22 Feb 2023
Protocol Amendment Number and Date:	Amendment #8
Date:	29 January 2024

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); however, sites located in the European Economic Area, the United Kingdom, and Switzerland are not included under the IND application and are not considered to be IND application sites.

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 of Technical Requirements for Pharmaceuticals for Human Use (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 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.

PROTOCOL SYNOPSIS

Title:	A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL)
Indication:	Adult subjects with relapsed or refractory (r/r) B-cell iNHL of follicular lymphoma (FL) or marginal zone lymphoma (MZL) histological subtypes.
Study Design:	Study KTE-C19-105 is a Phase 2, multicenter, single-arm, open-label study of axicabtagene ciloleucel in subjects with r/r iNHL. Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set**,** will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6 autologous, genetically modified, anti-CD19 chimeric antigen receptor (CAR) T cells per kg body weight. Each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • Conditioning chemotherapy • Investigational product (IP) treatment • Post-treatment assessment • Long-term follow-up
Study Objectives:	The primary objective is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR), in subjects with relapsed or refractory (r/r) B-cell iNHL. Key secondary objectives are to characterize the safety profile, complete response (CR) rate, ORR among those subjects with 3 or more lines of prior therapy, CR rate among those subjects with 3 or more lines of prior therapy, and to determine duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Additional secondary objectives will include additional safety and pharmacokinetic/pharmacodynamic endpoints and the time to next therapy endpoint.

Hypothesis:	Four hypotheses will be tested using a fixed sequence procedure in terms of ORR and CR to control the overall type I error at 1-sided alpha level of 0.025 with the following test order: Hypothesis 1 (H_1): test for ORR as determined by central review, if significant then Hypothesis 2 (H_2): test for CR rate as determined by central review, if significant then Hypothesis 3 (H_3): test for ORR as determined by central review in the subjects who have had 3 or more prior lines of therapy, if significant then Hypothesis 4 (H_4): test for CR rate as determined by central review in the subjects who have had 3 or more prior lines of therapy The hypotheses H_1 through H_4 will be assessed at the time of the interim analysis 3, 4, and 5 and the primary analysis. The H_1 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with the FL histological subtype in the inferential analysis set. The H_2 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with the FL histological subtype in the inferential analysis set. The H_3 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set who have had 3 or more prior lines of therapy. The H_4 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL the inferential analysis set who have had 3 or more prior lines of therapy. No formal hypothesis testing is planned for MZL histological subtype. The analysis will be descriptive.
Primary Endpoint:	ORR, defined as complete response (CR) + partial response (PR) per the Lugano Classification {Cheson 2014} as determined by central review. These assessments will be referred to as “central read” in this document.

Secondary Endpoints:	• CR rate, defined as CR per the Lugano Classification {Cheson 2014} by central read • ORR, defined as CR + PR per the Lugano Classification {Cheson 2014} by central read for those subjects who have had 3 or more prior lines of therapy • CR rate, defined as CR per the Lugano Classification {Cheson 2014} by central read for those subjects who have had 3 or more prior lines of therapy • Incidence of adverse events (AEs) and clinically significant changes in laboratory values • DOR • PFS • OS • Incidence of antibodies to axicabtagene ciloleucel • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum • Time to next therapy
Key Covariates for ORR and Other Key Safety and Efficacy Endpoints:	• Age (< 65, ≥ 65 years) • Gender • Race • Ethnicity • Relapsed vs refractory disease status at study entry • Follicular Lymphoma International Prognostic Index (FLIPI) score • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 • Time to relapse from initiation of first anti-CD20-chemotherapy combination therapy (≥ 24 months vs < 24 months) • Disease burden, as defined by Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria • Histological diagnosis by both local and central pathology • Prior PI3K inhibitor • Number of prior lines of therapy (excluding single agent anti-CD20 antibody as a line of therapy) • Double refractory (subjects refractory to the first 2 lines of therapy)

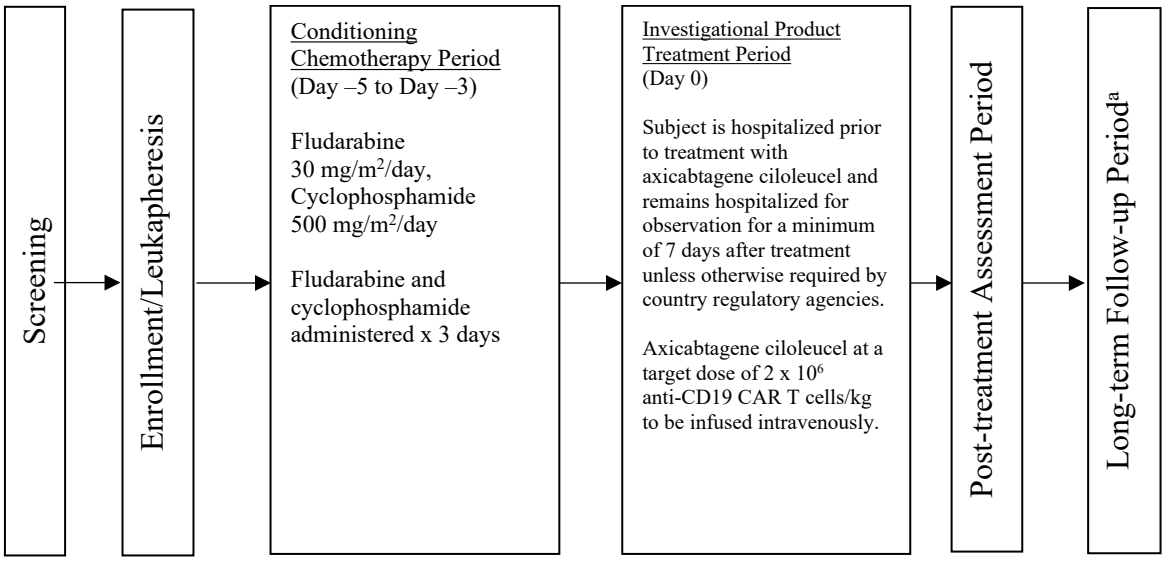
Sample Size:	Up to approximately 160 enrolled and treated subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set.
Duration of Study Participation	The duration of study participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, and survival. After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968 where they will complete the remainder of the 15 year follow-up assessments. Additional information is available in Section 3.5.
Study Eligibility:	Refer to Section 5 for a detailed list of inclusion and exclusion criteria.
Treatment (IP):	Axicabtagene ciloleucel treatment consists of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. Refer to Section 6 for treatment details.
Conditioning Chemotherapy Treatment:	Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.
Procedures:	At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures: collection of informed consent; general medical history, including previous treatments for B-cell iNHL; physical exam (including neurological exam), including vital signs and performance status; blood draws for complete blood count (CBC); chemistry panels; cytokines; C-reactive protein; lymphocyte subsets; antibodies to axicabtagene ciloleucel; replication-competent retrovirus (RCR); and anti CD19 CAR T-cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test. Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), a positron emission tomography-computed tomography (PET-CT), possible bone marrow aspirate and biopsy, and leukapheresis.

Data Safety Monitoring Board:	An independent Data Safety Monitoring Board (DSMB) will have ongoing oversight of the study and will monitor data during this study. The DSMB will first meet to review safety data when 10 subjects are enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 30 subjects are enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 30 subjects with FL in the inferential set are enrolled and treated with axicabtagene_ciloleucel and have had an opportunity to be followed for 6 months from the date of axicabtagene_ciloleucel infusion. The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months from the date of axicabtagene ciloleucel infusion. The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed. Refer to Section 9.9.
Statistical Considerations:	The primary endpoint for the study is ORR per the Lugano Classification {Cheson 2014} as determined by central read. The study will enroll and treat up to approximately 160 subjects including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential set. The study uses a single-arm design of the subjects with FL in the inferential analysis set to test for an improvement in response rates (ORR and CR rate), with descriptive analyses being conducted for the subjects with MZL. For the test of primary efficacy in at least 80 subjects with FL in

	the inferential analysis set, this study has approximately 93% power to test the null hypothesis that the ORR is 40% versus the alternative hypothesis that the ORR is 60% with a 1-sided alpha level of 0.0237. The following planned analyses will be performed. • Interim analysis 1 will be conducted after 10 subjects in the safety analysis set (Section 10.5) have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only. • Interim analysis 2 will be conducted after 30 subjects in the safety analysis set (Section 10.5) have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only. • Interim analysis 3 will be performed when 30 subjects in the FL inferential set have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. This interim analysis will be for safety and to assess early demonstration of efficacy. This interim analysis is based on the interpolated alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.0003. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive. • Interim analysis 4 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy for this analysis is 0.0005. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive. • Interim analysis 5 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 9 months after the first disease assessment. The nominal alpha level for the assessment of efficacy for this analysis is 0.0005. The study will not be stopped if early efficacy is demonstrated. The analyses of the efficacy endpoints for MZL will be descriptive.

	• The primary analysis will occur after at least 80 subjects with FL in the inferential analysis set have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 12 months after the first disease response assessment. • Follow-up analysis 1 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 18 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy and will be descriptive. • Follow-up analysis 2 will be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 24 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy and will be descriptive. • Additional follow-up analyses may be performed as needed to satisfy regulatory requirements, and to perform long-term efficacy, safety, and survival follow-up. • The final analysis will occur after all subjects transition to the LTFU study, KT-US-982-5869.

Figure 1. Study Schema



Abbreviations: CAR, chimeric antigen receptor.

a. Long-term Follow-up Period: After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will complete the remainder of the 15 year follow-up assessments in a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EU	European Union
FAS	Full analysis set
FER	Ferritin
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GELF	Groupe d'Etude des Lymphomes Folliculaires

GM-CSF	Granulocyte macrophage-colony stimulating factor
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic-pyruvic transaminase
HDT	High-dose chemotherapy
HEENT	Head, eyes, ears, nose, and throat
Hep	Hepatitis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification
IFN	Interferon
IL	Interleukin
iNHL	Indolent non-Hodgkin lymphoma
IP	Investigational product
IPI	International Prognostic Index
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
r/r	Relapsed or refractory

SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplantation
SD	Stable disease
SmPC	Summary of product characteristics
SOA	Schedule of assessment
SUSAR	Suspected unexpected serious adverse reaction
TBI	Total body irradiation
TFL	Transformed follicular lymphoma
TNF	Tumor necrosis factor
UE	Unevaluable
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

The primary objective is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR), in subjects with relapsed or refractory (r/r) B-cell iNHL.

Key secondary objectives are to characterize the safety profile, complete response (CR) rate, ORR among those subjects with 3 or more lines of prior therapy, CR rate among those subjects with 3 or more lines of prior therapy, and to determine duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Additional secondary objectives will include additional safety and pharmacokinetic/pharmacodynamic endpoints and the time to next therapy endpoint.

2. DISEASE BACKGROUND AND RATIONALE

Indolent non-Hodgkin lymphomas comprise approximately one-third of malignant lymphomas {Gribben 2007}. Their presentation is typically insidious, with slow-growing lymphadenopathy, organomegaly, and cytopenias. Systemic B symptoms (fever, weight loss, night sweats) and spontaneous tumor lysis or other oncologic emergencies are uncommon during initial stages {Freedman 2018, Gribben 2007, Tan 2013}. The indolent lymphomas are further subdivided by histology, with FL, MZL (inclusive of splenic, nodal, and mucosa-associated lymphoid tissue subtypes), and small lymphocytic lymphoma making up the bulk of diagnoses {Al-Hamadani 2015, Lunning 2012, The Non-Hodgkin's Lymphoma Classification Project 1997}.

FL is the most common iNHL and represents approximately 17% of non-Hodgkin lymphoma (NHL) cases in the United States {Al-Hamadani 2015}, with an incidence of 3.5 new cases per 100,000 person years {Noone 2017}. Like most iNHL subtypes, it is largely considered to be incurable with standard front-line therapies {Wang 2017}. However, advances in the management of this disease over the last several decades have led to a substantial improvement in long-term survival, with 1 retrospective analysis demonstrating a median OS of nearly 20 years from first diagnosis {Tan 2013}.

Despite these strides made in managing FL, outcomes in FL are quite varied {Kahl 2016}. Prognosis of newly diagnosed FL is predicted by one of several clinical risk stratification scores, such as the Follicular Lymphoma International Prognostic Index (FLIPI) {Solal-Céligny 2004} and the FLIPI-2 {Federico 2009}. These scores are adaptations of the International Prognostic Index (IPI) used in aggressive lymphomas and have been shown to stratify patients by outcome into low-, intermediate-, or high-risk subsets. High-risk patients with ≥ 3 FLIPI criteria have a 5-year overall survival rate of 53%, whereas, low-risk patients with ≤ 1 FLIPI criterion have a 5-year survival rate of over 90%.

Patients with limited stage disease may benefit from involved field radiation therapy, chemotherapy, and rituximab, or, in patients who are ineligible for radiation therapy due to disease site, observation {Freedman 2018}. Low-risk patients with advanced stage disease may also be eligible for a period of close disease observation with regular imaging assessments {National Comprehensive Cancer Network 2018}. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria are commonly used to trigger treatment in such patients. These criteria include bulky disease, B symptoms, splenomegaly, pleural effusions, peritoneal ascites, cytopenias, and leukemia (> 5.0 x 10^9/L malignant cells) {Brice 1997, National Comprehensive Cancer Network 2018}. Patients with indications for systemic therapy are generally treated with one of a variety of regimens shown in Table 1.

Table 1. Treatment Outcomes in First-line Indolent Lymphoma

Regimen	N	Outcome	Reference
Rituximab + bendamustine	514	Improved PFS vs R-CHOP (69.5 m vs 31.2 m)	{Rummel 2013}
Rituximab + CHOP	38	ORR 100%; DOR 83.5 months	{Czuczman 2004}
Rituximab + CVP	321	Improved TTP vs CVP (34 m vs 15 m)	{Marcus 2008}
Rituximab (maintenance)	379	Improved 3-year PFS vs observation (82% vs 36%)	{Ardeshna 2014}
Rituximab + lenalidomide	103	ORR 90%; 3-year PFS 75.3%	{Fowler 2014}

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, prednisone; DOR, duration of response; m, months; N, number; ORR, overall response rate; PFS, progression-free survival; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; TTP, time to progression.

ORRs with front-line chemoimmunotherapy with an alkylator and anti-CD20 monoclonal antibody combination are nearly 100% {Flinn 2014}. However, Casulo and colleagues recently showed that among 588 patients with FL who received first-line R-CHOP, approximately 20% relapsed within 2 years of diagnosis {Casulo 2015}. Importantly, these patients had significantly worse outcomes overall, with 2-year OS of 64% and 5-year OS of 50%, respectively. In contrast, patients without early disease progression had 5-year OS rates of 90%.

Similar findings were reported by Maurer and colleagues, who examined cases from the Mayo Clinic-University of Iowa Specialized Programs of Research Excellence Molecular Epidemiology Resource (SPORE MER) {Maurer 2016}. Their analysis demonstrated that 17% of patients treated with front-line combination chemotherapy with rituximab did not achieve event-free survival (EFS) at 12 months and 29% of patients did not achieve EFS at 24 months. These patients had poor OS outcomes, because they showed increased mortality when compared with an age- and sex-matched control group drawn from the US general population. By contrast, patients who achieved EFS at 12 months and 24 months had mortality rates that were comparable to rates observed in the control population.

These studies reveal a population of patients who are not accurately identified by existing pretreatment prognostication tools like the FLIPI. Whether current standard high-intensity salvage strategies, such as autologous stem cell transplantation (ASCT), can improve long-term survival outcomes remains to be determined. Therefore, patients with FL who experience disease progression within 2 years of diagnosis and treatment with rituximab and chemotherapy represent a group with high need for new and efficacious treatments.

Another group of patients with a high unmet medical need consists of patients with iNHL who have relapsed following more than 1 line of combination chemotherapy, particularly those who progress rapidly following treatment. Patients with iNHL who progress soon (eg, 6 months) after completing treatment are frequently referred to as refractory to agents contained in the regimen. Such patients may be refractory to chemotherapy, rituximab, or both, and tend to have incomplete and short-lived responses.

In 2014, a PI3Kδ inhibitor, idelalisib, was conditionally approved for use by the Food and Drug Administration (FDA) in patients who have relapsed with FL based on published data {Gopal 2014, ZYDELIG 2016}. In this study, 125 patients who were refractory to rituximab and an alkylating agent (defined as lack of response or had experienced relapse within 6 months of completing therapy) were given idelalisib 150 mg twice daily until disease progression, unacceptable drug toxicity, or patient death. The ORR in the overall population was 57%, with 6% achieving a CR. The ORR in FL was 54% (39/72), and in MZL, it was 47% (7/15). The median PFS was 11 months, with a 12-month PFS rate of < 50%, highlighting the need for new therapies.

The drug was associated with significant gastrointestinal side effects with 43% of all treated patients experiencing any grade diarrhea (13% Grade 3 or higher) and 30% reporting nausea. Additionally, Grade 3 or higher elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were seen in 13% and 8% of patients, respectively. Cytopenias were common as well: 27% of patients had Grade 3 or higher neutropenia, and reductions in hemoglobin and platelets were each seen in roughly a quarter of patients. Treatment was discontinued due to adverse events (AEs) in 25 patients (20%), and 42 patients (34%) required dose reductions. Eleven patients died while receiving the study drug or within 30 days of discontinuation.

In 2017, a second PI3K inhibitor (PI3Kδ and PI3Kα inhibitor), copanlisib, received an accelerated approval by the FDA in patients who have relapsed with FL based on published data {ALIQOPA 2017, Dreyling 2017}. In this study, 142 patients with iNHL who had > 2 prior lines of therapy were enrolled; 104 of these patients had FL. Copanlisib was given intravenously at a dose of 60 mg on Day 1, Day 8, and Day 15 of a 28-day cycle. The ORR in the overall population was 59%, with 12% achieving a CR. The median PFS was 11.2 months, and median DOR was 22.6 months. The ORR in FL was 59% (61/104), and the ORR in MZL was 70% (16/23). The drug was associated with significant side effects, with 41% of patients experiencing Grade 3 or higher hyperglycemia, and 24% experiencing Grade 3 hypertension (> 160 mm Hg). Cytopenias were noted, with 24% of patients Grade 3 or higher neutropenia, and 7% experiencing Grade 3 or higher thrombocytopenia. Grade 3 or higher lung infection was observed in 16% of patients.

A number of agents, which are under investigation in relapsed FL, are summarized in {Kahl 2016} and presented in Table 2.

Table 2. Investigational Treatments in Relapsed or Refractory iNHL

Agent	Classification	N	ORR (%)	CR (%)	PFS/TTP	Reference
Lenalidomide vs Lenalidomide + rituximab	Immunomodulator vs Immunomodulator + anti-CD20 mAb	45 46	53 76	20 39	mTTP (y) 1.1 2	{Leonard 2015}
Duvelisib (IPI-145)	PI3K-δ and PI3K-γ inhibitor	83	41	0	mPFS (mo) 8.3	{Flinn 2016}
Ibrutinib	BTK inhibitor	40	37.5	12.5	mPFS (mo) 14	{Bartlett 2018}
Venetoclax (ABT-199)	BCL-2 inhibitor	29	37.9	13.8	mPFS (mo) 11	{Davids 2017}
Polatuzumab vedotin + Rituximab	Anti-CD79b antibody-drug conjugate 2.4 mg/kg 1.8 mg/kg: + anti-CD20 mAb	25 20	76 75	44 10	mPFS (mo) 15 Not reached	{Advani 2015}
Obinutuzumab vs Rituximab	Anti-CD20 mAbs: Obinutuzumab Rituximab	74 75	44.6 33.3	NR NR	mPFS (mo) 17.6 25.4	{Sehn 2015}

Abbreviations: BCL-2, B-cell lymphoma-2; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CR, complete response; mAb. mo, month; mPFS, median progression-free survival; mTTP, median time to progression; N, number; NR, not reported; ORR, objective response rate; y, year.
Note: Table adapted from {Kahl 2016}

High-dose chemotherapy (HDT) followed by ASCT is an option for patients who experience a disease relapse, and can result in subsequent remissions. Randomized data from the pre-rituximab era suggests improved PFS and OS for patients with relapsed FL who are treated with HDT/ASCT vs those who are treated with conventional chemotherapy alone {Schouten 2003}. Retrospective single-institution data suggest that HDT/ASCT is associated with improved survival outcomes in patients with < 3 previous chemotherapies or low FLIPI scores compared with patients who had ≥ 3 prior chemotherapies or high FLIPI scores {Vose 2008}. This finding is supported in the setting of myeloablative therapy followed by ASCT in a retrospective study of patients treated at Dana Farber Cancer Institute and St. Bartholomew's Hospital {Rohatiner 2007}. This conditioning regimen yielded durable remissions, as 48% of patients were disease-free after 10 years of follow-up. Further, after 12-years of follow-up, the remission duration curve plateaued at 48%, suggesting that some patients may be cured of their lymphoma with this treatment approach. However, this therapy was associated with a high risk of secondary myeloid dysplasia or acute myeloid leukemia, which resulted in 15 deaths in this study. The risk of the development of a secondary myeloid neoplasm is further underscored by Friedberg and colleagues {Friedberg 1999} in which the actuarial incidence of myelodysplastic syndrome (MDS) at 10 years following ASCT after cyclophosphamide/total body irradiation (TBI) was nearly 20%. Furthermore, outcomes following diagnosis of MDS in this population were dismal, with the majority of patients exhibiting poor-risk cytogenetics and a median OS of 9.4 months.

The role of allogenic transplantation in relapsed FL is not clear. Evens and colleagues showed similar failure-free survival, but inferior overall survival, due to increased nonrelapse mortality in patients treated with allogenic transplant compared with those treated with ASCT in the rituximab era {Evens 2013}. Reducing the conditioning regimen for allogenic transplant does not seem to alleviate the treatment-related mortality, as shown in a larger retrospective study in which the 3-year nonrelapse mortality was 5% and 22% for ASCT and reduced-intensity allogenic transplant, respectively {Robinson 2013}. Nevertheless, a small, retrospective, single-institution study suggested that patients with a remission duration of ≤ 12 months prior to initiating salvage therapy may show improved disease control and EFS with allogeneic transplant compared with ASCT {Lunning 2016}.

Although currently available therapies for relapsed/refractory iNHL show some benefit, additional therapies are needed. Anti-CD19 chimeric antigen receptor (CAR) T cells with CD28 and CD3ζ signaling domains have shown promising activity in patients with B-cell cancers. While the majority of patients treated with CAR T cells thus far have had aggressive lymphoma and B-cell precursor leukemia, small numbers of subjects with indolent B-cell lymphomas have also been treated. In 2009, Kite Pharma, Inc., (hereafter referred to as Kite or Kite Pharma) initiated a clinical trial in partnership with the National Cancer Institute (NCI; #NCT00924326) using CAR T cells in subjects with NHL and chronic lymphocytic leukemia (CLL). The CAR T cells in the NCI study were manufactured using the same CAR construct used in axicabtagene ciloleucel. Of the 43 subjects who were treated on that protocol, 7 subjects had iNHL {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017}. The subjects with iNHL had a median age of 57 and a median of 3 prior therapies. Study treatment for the first 4 subjects with iNHL was more intense than current designs and consisted of conditioning chemotherapy with cyclophosphamide (60 to 120 mg/kg) for 2 days followed by fludarabine (25 mg/m^2) for 5 days. This conditioning regimen was followed by a single infusion of 3, 11, 13, or 30 x 10^6 anti-CD19 CAR T cells/kg, which was then followed by high dose interleukin (IL)-2 (720000 IU/kg every 8 hours for 4 to 10 doses, where toxicity precluded additional doses) {Kochenderfer 2012}.

The remaining 3 subjects received CAR T cells generated with an improved short-term culture method (6 to 10 days), at 1, 1, or 2 x 10^6 anti-CD19 CAR T cells/kg, respectively, and received and no post infusion IL-2 {Kochenderfer 2015, Kochenderfer 2017}. One subject received a relatively high dose of conditioning chemotherapy, with 120 mg/kg cyclophosphamide {Kochenderfer 2015}. Two subjects received less intense conditioning chemotherapy, with cyclophosphamide (300 or 500 mg/m^2) for 3 days and with fludarabine (25 mg/m^2) for 3 days {Kochenderfer 2017}.

The ORR and CR rate in the 6 subjects with iNHL evaluable for efficacy was 6/6 (100%) and 4/6 (67%), respectively. At the time of the data cutoff in December 2015, at a median follow-up of 24.9 months, 5/6 subjects with iNHL remained in response with a median DOR of 23.9 (11+ to 64.6+) months. Grade ≥ 3 CAR-related AEs occurred in 50% of subjects; Grade ≥ 3 CAR-related cytokine release syndrome (CRS) and neurotoxicity AEs occurred in 29% and 36% of subjects, respectively. All AEs resolved without routine use of tocilizumab or steroids. There were no CAR-related deaths.

Recently, a CAR T-cell study (utilizing a different anti-CD19 CAR) in lymphoma has reported outcomes for 14 patients with FL. This study utilized the University of Pennsylvania CAR construct of anti-CD19 single-chain variable fragment (scfv) fused to a fragment of the 4-1BB costimulatory molecule and the CD3 zeta chain. Ten of 14 patients (71%) achieved a CR at 6 months. Importantly, these responses were maintained, as none of the patients who achieved a CR at 6 months had relapsed at the time of publication (median follow-up of 28.6 months) {Schuster 2017}.

These results suggest that anti-CD19 CAR T cells may help to meet the unmet medical need for effective treatments of relapsed/refractory iNHL.

2.1. CD19 Target Expression

CD19 is a 95 kD transmembrane protein expressed only in the B-cell lineage. It is expressed in all normal B cells starting at the pro-B-cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells. The pattern of CD19 expression is maintained in B-cell malignancies, including all subtypes of B-cell NHL, CLL, and non-T-cell acute lymphoblastic leukemia (ALL) {Blanc 2011} with the exception of multiple myeloma.

2.2. Anti-CD19 Chimeric Antigen Receptor T-cell Product

Axicabtagene ciloleucel is an autologous cell therapy product being developed by Kite Pharma. Patient T cells are redirected to recognize CD19 by transducing them with an anti-CD19 CAR. The CAR vector construct utilized in axicabtagene ciloleucel is identical to the one used in NCI protocols (Surgery Branch Protocol 09-C-0082; IND: 13871; Pediatric Branch Protocol 12-C-0112G; IND: 14985). The anti-CD19 CAR vector construct has been designed, optimized, and initially tested at the Surgery Branch of the NCI (Figure 2) {Kochenderfer 2009, Kochenderfer 2010a, Kochenderfer 2010b}.

The anti-CD19 CAR has been engineered to express an extracellular single-chain variable fragment (scFv) with specificity for CD19, linked to an intracellular-signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 co-stimulatory molecule, including the intracellular-signaling domain, is added to the signaling domain of the CD3ζ chain, which is required for T-cell activation {Kowolik 2006}.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. CCI [redacted] Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

Refer to the current axicabtagene ciloleucel Investigator's Brochure (IB) for additional descriptions of the T-cell product.

2.3. Axicabtagene Ciloleucel Experience in Diffuse Large B-cell Lymphoma (ZUMA-1 Trial)

ZUMA-1 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in adult subjects with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). The primary analysis for the study, which has been completed, was based on analysis of the data from 101 subjects who had been followed for at least 6 months after infusion of axicabtagene ciloleucel. The study met its primary endpoint: the ORR in these 101 subjects was 82% (95% confidence interval [CI]: 72% to 89%), which was significantly higher than the pre-specified control rate of 20% ($p < 0.001$). The CR rate was 52% {Neelapu 2017}. With a median follow-up of 15.4 months, 42% of subjects had ongoing durable responses.

Refer to the current axicabtagene ciloleucel IB for a summary of the safety and efficacy findings from this study.

2.4. Other Axicabtagene Ciloleucel Study Results

Refer to the current axicabtagene ciloleucel IB for current study results.

2.5. Benefit/Risk Assessment for the Study

Refer to the current version of the IB for a summary of the known and potential benefits and risks associated with axicabtagene ciloleucel.

3. STUDY DESIGN

3.1. General Study Design

Study KTE-C19-105 is a Phase 2, multicenter, open-label study evaluating the efficacy of axicabtagene ciloleucel in subjects with r/r B-cell iNHL of FL or MZL histological subtypes.

Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2×10^6 anti-CD19 CAR T cells per kg body weight.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up (LTFU)

An independent Data Safety Monitoring Board (DSMB) will have ongoing oversight of this study and will review data during this study. The DSMB will first meet to review safety data when 10 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet for a second time to review safety data after 30 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet for a third time to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months. The DSMB will meet for a fourth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB will meet for a fifth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment.

The DSMB will also review serious adverse event (SAE) information and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout the study. The DSMB may meet more often as needed.

For details surrounding the DSMB, refer to Section 9.9.

For study requirements assigned to each study period, refer to the schedule of assessments (SOA; Table 3 and Table 4) and Section 7 for details.

A study schema is represented in Figure 1.

3.2. Participating Sites

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

Sites that do not enroll a subject within 3 months of their site being activated will be considered for closure.

3.3. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated in this study.

Refer to Section 10 for statistical considerations, including sample size estimations.

3.4. Replacement of Subjects

Clinical trial subjects will continue to be enrolled until the specified numbers are attained in the safety analysis and inferential analysis sets. Subjects who have not received axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (see Section 10.5).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and if applicable, timing of transition to the separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968. After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to the LTFU study.

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject transitions to the LTFU study or, while still a participant in this study, is considered lost to follow-up, withdraws consent, or dies. Upon activation of the LTFU study at the subject's study site, the subject will complete LTFU assessments under the LTFU protocol.

3.6. Long-term Follow-up

After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will transition to the LTFU study where they will complete the remainder of the 15 year follow-up assessments. On the LTFU study, subjects will be monitored for the occurrence of late-onset targeted AEs/serious AEs (SAEs) suspected to be possibly related to axicabtagene ciloleucel, occurrence of any product-related SAEs and presence of replication-competent retrovirus (RCR) and/or insertional mutagenesis.

In the LTFU study, subjects will continue assessments at timepoints contiguous with their timepoints in this study.

4. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved consent form before initiating any study-specific procedures or activities that are not part of a subject's routine care. Refer to Section 7 for details.

Each subject who enters the screening period will receive a unique subject identification (ID) number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

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 or retreated.

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

1) Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal or extranodal, based on criteria established by the World Health Organization (WHO) 2016 classification

2) Relapsed or refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. (Single agent anti-CD20 antibody will not count as line of therapy for eligibility.) Stable disease (without relapse) > 1 year from completion of last therapy is not eligible.

3) 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.

4) No known history or suspicion of central nervous system (CNS) involvement by lymphoma.

5) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy and enrollment, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and enrollment (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists).

6) Toxicities due to prior therapy must be stable and recovered to ≤ Grade 1 (except for clinically non-significant toxicities, such as alopecia).

7) Age 18 or older

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

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

10) Platelet count ≥ 75000/uL

11) Absolute lymphocyte count ≥ 100/uL

12) Adequate renal, hepatic, pulmonary, and cardiac function defined as:

    a) Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min

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

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

    d) Left ventricular ejection fraction (LVEF) ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant arrhythmias

e) No clinically significant pleural effusion

f) Baseline resting oxygen saturation > 92% on room air

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

5.2. Exclusion Criteria

1) Transformed FL or MZL

2) Small lymphocytic lymphoma

3) FL Histological Grade 3b

4) Lymphoplasmacytic lymphoma

5) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free and without anticancer therapy for at least 3 years.

6) ASCT within 6 weeks of planned axicabtagene ciloleucel infusion

7) History of allogeneic stem cell transplantation

8) Prior CD19 targeted therapy, with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for retreatment

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

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

11) Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management.

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

13) Presence of lymphoma that is known to involve the full thickness of the gastric wall.

14) Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted.

15) Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases or with a history of cerebrospinal fluid (CSF) malignant cells or brain metastases

16) History or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome (PRES), or any autoimmune disease with CNS involvement

17) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

18) History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months of enrollment

19) Possible requirement for urgent therapy within 6 weeks after leukapheresis due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

20) History of autoimmune disease (eg, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus), resulting in end organ injury or requiring systemic immunosuppression or systemic disease modifying agents within the last 2 years. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and subjects with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

21) History of symptomatic deep vein thrombosis (DVT) or pulmonary embolism within 6 months of enrollment. History of upper extremity line related DVT within 3 months of conditioning chemotherapy.

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

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

24) Treatment with a live, attenuated vaccine within 6 weeks prior to the planned start of the conditioning regimen or anticipation of need for such a vaccine during the course of the study

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

26) Subjects of either sex who are not willing to practice birth control from the time of consent through 12 months following conditioning chemotherapy administration or 12 months following axicabtagene ciloleucel infusion, whichever is longer.

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

6. PROTOCOL TREATMENT

6.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The IP for this study is named axicabtagene ciloleucel.
- The term study treatment refers to all protocol-required therapies.

6.2. Study Treatment

6.2.1. Axicabtagene Ciloleucel

This section contains general information about axicabtagene ciloleucel and is not intended to provide specific instructions. Refer to the Investigational Product Manual (IPM) for details and instruction on storing, thawing, and administering axicabtagene ciloleucel.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing axicabtagene ciloleucel arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen, and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusing 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, initials, 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. The product must not be thawed until the subject is ready for the infusion.

There have been no instances of accidental overdose of subjects in this program. 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 to any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject ID labels) in this study are identified, clinical site staff should report the problem per the instructions in the IPM.

6.2.2. Auxiliary/Non-Investigational Medicinal Products

All other medications described throughout the Protocol are considered auxiliary or non-investigational medicinal products. These products are used in accordance with their authorized product information in any given country (eg, Package Insert, Summary of product characteristics [SmPC]) and institutional guidelines. The identified and potential risks, and risk minimization, should be managed as described within either the authorized product information and/or in accordance with institutional guidelines. A list of all auxiliary/non-investigational medicinal products is provided in Appendix 18.4.

6.2.2.1. Conditioning Chemotherapy

Conditioning chemotherapy will be supplied by the investigative site unless otherwise noted. Conditioning chemotherapy should only commence when the product is available, if required by country regulatory agencies. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of both agents.

Subjects will receive a conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, administered x 3 days to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo.

6.2.2.1.1. Fludarabine

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

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

6.2.2.1.2. Cyclophosphamide

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

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

6.2.2.1.3. Mesna

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

administered around the cyclophosphamide dose according to institutional standards. Refer to the most recent version of the package insert for specific details surrounding the administration of mesna.

6.2.2.2. Concomitant Therapy

Investigators may additionally prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF; granulocyte colony stimulating factor) and routine anti-emetic prophylaxis and treatment, except those medications listed in the excluded medications in Section 6.2.2.3.

All concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent through 3 months after completing treatment with axicabtagene ciloleucel. After 3 months of follow-up, only targeted concomitant medications will be collected for 24 months after axicabtagene ciloleucel infusion or disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

For subjects who are not enrolled (eg, screen failure or who do not undergo leukapheresis), only concurrent therapies related to any SAE(s) will be recorded.

For subjects who are enrolled, but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy). Specific concomitant medications collection requirements and instructions are included in the case report form (CRF) completion guidelines.

6.2.2.3. 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 prior to leukapheresis and 5 days prior to axicabtagene ciloleucel administration.

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

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration unless used to manage axicabtagene ciloleucel-related or other severe toxicities (eg, anaphylaxis). Other medications that might interfere with the evaluation of axicabtagene ciloleucel, such as non-steroidal 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.

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

6.2.3. 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 transplantation (SCT) and radiation therapy, will be recorded until one of the following happens: the subject transitions to the LTFU study, is considered lost to follow-up, withdraws consent, or dies.

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

6.3. Rationale for Study Treatment Dosing: Conditioning Chemotherapy and Axicabtagene Ciloleucel Dose

6.3.1. Conditioning Chemotherapy Dose

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific $CD8^+$ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine is a potent lymphodepleting regimen.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose will be cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days. Cyclophosphamide (500 mg/m^2) and fludarabine (30 mg/m^2) both given for 3 concurrent days have been studied and tolerated in subjects with B-cell malignancies {O'Brien 2001}. This regimen has been evaluated in the NCI study and is the dose of conditioning chemotherapy that is being studied in other studies in NHL at Kite.

6.3.2. Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on aggregate safety and efficacy data compiled from the KTE-C19-101 study as outlined in the axicabtagene ciloleucel IB. Based on the favorable benefit/risk ratio observed in KTE-C19-101, a target dose of 2×10^6 anti-CD19 CAR T cells/kg will be used for this protocol.

6.4. Study Treatment Schedule

6.4.1. Leukapheresis

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells [WBCs]) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the cell processing facility (CPF) overnight as described in the IPM.

Mononuclear cells will be obtained by leukapheresis CCI [redacted] The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

CCI [redacted] T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF standard operating procedures (SOPs). After the product has passed certain release tests, it will be shipped to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

6.4.2. Cyclophosphamide and Fludarabine (Days –5 Through –3 Before Infusion of Axicabtagene Ciloleucel)

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day –5 through Day –3 with 2 rest days before the receiving axicabtagene ciloleucel. The 3-day conditioning chemotherapy regimen will be administered in an outpatient setting, as follows:

- IV hydration with 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion (and as needed, according to local institutional guidelines) followed by:
- Cyclophosphamide 500 mg/m^2 IV over 60 minutes (± 15 minutes) followed by:
- Fludarabine 30 mg/m^2 IV over 30 minutes (± 15 minutes) followed by:
- An additional 1 L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add mesna per institutional guidelines

At investigator discretion, an alternative balanced crystalloid can be used in place of 0.9% NaCl. Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general, subjects should be kept well hydrated, but closely monitored to prevent fluid overload.

6.4.3. Axicabtagene Ciloleucel (Day 0)

All subjects will be hospitalized to receive treatment with axicabtagene ciloleucel followed by an observation period. Subjects will remain in the hospital at a minimum through Day 7 post-treatment with axicabtagene ciloleucel unless otherwise required by country regulatory agencies. Refer to Section 18.3 for more information.

Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to ≤ Grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1 or if deemed necessary by the treating investigator.

6.4.3.1. Axicabtagene Ciloleucel Premedication Dosing

The following axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion. Alternatives to the recommendations below should be discussed with the Kite medical monitor.

- Acetaminophen 650 mg PO (eg, Tylenol)
- Diphenhydramine 12.5 to 25 mg IV or PO (eg, Benadryl)

6.4.3.2. Axicabtagene Ciloleucel Dosing

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel and for the hospitalization treatment period. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the IPM. The IPM must be reviewed prior to administration of axicabtagene ciloleucel.

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

6.5. Toxicity Management

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

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important that you always refer to the most current version of the axicabtagene ciloleucel IB for guidance regarding managing axicabtagene ciloleucel-related toxicities.

Additional information and management recommendations can also be found in the IB regarding important potential risks associated with axicabtagene ciloleucel as well as possible complications associated with malignancy and cancer treatment.

7. STUDY PROCEDURES

Research staff should refer to the SOAs in Table 3 and Table 4 for an outline of the procedures required. The visit schedule is calculated from axicabtagene ciloleucel infusion on Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7.11. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

7.1. Informed Consent

Before a subject's participation 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 the potential risks. Subjects should sign the most current IRB/IEC approved informed consent form (ICF) prior to any study-specific activity or procedure is performed.

The consent process and the 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 ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

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

7.2. Demographic Data

Demographic data will be collected to include sex, age, race, and ethnicity.

7.3. Medical and Treatment History

Relevant medical history prior to the start of AE reporting will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition that would be typically shared in a referral letter. All findings will be recorded in the CRFs.

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 research center, copies from the subject's chart should be obtained and reviewed.

7.4. Physical Exam, Vital Signs, Performance Status

Physical exams, including neurological exam, will be performed during screening and at times noted in the SOA (refer to Table 3 and Table 4). Changes noted in subsequent exams when compared to the baseline exam will be reported as an AE.

During IP administration/hospitalization, vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, will be monitored before and after the axicabtagene ciloleucel infusion and then routinely (every 4 to 6 hours) while hospitalized. If the subject has a fever (temperature 38.3˚C or greater) at any time during hospitalization, vital signs will be monitored more frequently as clinically indicated.

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

7.5. Bone Marrow Biopsy

Bone marrow aspirate and biopsy will be performed at screening, if not previously performed, to assess bone marrow involvement.

A repeat bone marrow aspirate and biopsy will be required to confirm a complete response to axicabtagene ciloleucel except among subjects known to be negative for bone marrow involvement.

To confirm a 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 18.3 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}.

7.6. Lumbar Puncture

Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture performed at the screening visit for examination of CSF. In addition, lumbar puncture should be performed for subjects with new onset of ≥ Grade 2 neurological event (see the axicabtagene ciloleucel IB) after axicabtagene ciloleucel infusion. Opening pressures for all lumbar punctures (LPs) should be measured and recorded in the subject's site record whenever possible.

7.7. Disease Response Assessment

Disease assessments will be evaluated for response per the Lugano Classification {Cheson 2014} by the site investigator at times indicated in the SOA (refer to Table 3 and Table 4). All enrolled subjects will be monitored via fluorodeoxyglucose positron emission tomography (FDG–PET) with diagnostic quality contrast-enhanced CT and/or other scans as specified in the imaging manual. Scans will be sent to a central imaging vendor to be reviewed by an independent central reviewer using the Lugano Classification {Cheson 2014}.

For subjects who discontinue the study due to an assessment of progressive disease (PD), any additional imaging data, subsequent to the image in question, may also be submitted to the central imaging vendor. Refer to the study imaging manual for details regarding submission of scans to the imaging vendor.

Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

Baseline positron emission tomography-computed tomography (PET-CT) scans of the neck, chest, abdomen, and pelvis, along with the appropriate imaging of all other sites of disease, are required. Subjects will have their post-axicabtagene ciloleucel infusion planned PET-CT tumor assessments during the post-treatment and LTFU period per the SOA. Additional CT scans will be performed at regular intervals as highlighted in the SOA during the LTFU portion of the study.

Post-axicabtagene ciloleucel administration disease assessments will be used to determine the time when PD occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule according to the SOA.

For subjects with disease progression who are 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, provided it was done within 28 days of retreatment.

7.8. Cardiac Function

Each subject's cardiac function will be assessed by an electrocardiogram (ECG) and ECHO during the screening period to confirm study eligibility. Adequate LVEF and no evidence of pericardial effusion, as required by eligibility criteria, will be documented by ECHO. An ECHO performed following the subject's last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

7.9. Laboratory

The below samples will be collected at the time points indicated in the SOA (refer to Table 3 and Table 4). Additional samples (eg, blood, urine, CSF, tissue) may be collected, as needed, for additional safety testing.

7.9.1. Local Lab Analysis

- Sodium (Na), potassium (K), chloride (Cl), total CO2 (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin direct bilirubin, lactate dehydrogenase (LDH), uric acid

- C-reactive protein (CRP), ferritin (FER)

- Complete blood count (CBC) with differential (if WBC counts are adequate per the local lab)

- For European Union (EU) sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects 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 contact the Kite medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting the Kite medical monitor for instructions. See Section 9.6 for details.

7.9.2. Central Lab Analysis

- Blood draws for PBMC (lymphocyte subsets, replication-competent retrovirus [RCR], and anti-CD19 CAR T cells) and cytokine analysis will be performed at intervals outlined in the SOA (refer to Table 3 and Table 4).

- Serum samples will also be drawn for antibodies to axicabtagene ciloleucel.

  — For serum samples that demonstrate increased anti-axicabtagene ciloleucel antibodies at the Week 4 or Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or become negative) or up to 1 year from the completion of treatment, whichever occurs first. Samples that test positive in the screening enzyme-linked immunosorbent assay will undergo confirmatory analysis in a cell-based assay.

  — Archived tumor tissue will be collected for central confirmatory diagnosis, central pathology review, and evaluation of prognostic markers specific for iNHL and pertaining to the tumor immune environment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged.

  — Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations) or tumor/immune-related RNA and protein markers.

- CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments (refer to Table 3 and Table 4) and per Section 7.5 and Section 7.6.

- See central laboratory manual for details on sample collection, processing, and shipping instructions.

7.10. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate pharmacodynamic markers for axicabtagene ciloleucel. Prognostic markers specific for iNHL and related to the tumor immune microenvironment may also be evaluated in archived and fresh tumor biopsies.

The presence, expansion, persistence, and immunophenotype of the anti-CD19 CAR T cells will be monitored in the blood by flow cytometry. Expansion and persistence will also be monitored by an anti-CD19 CAR-specific quantitative polymerase chain reaction (qPCR) and/or flow cytometry.

Levels of serum cytokines will also be evaluated in the blood. CCI [redacted]

CSF, as well as any additional subject samples (eg, pleural fluid), may be collected from subjects who develop a neurological event or CRS to enable evaluation of inflammatory cytokines and chemokine levels and presence of anti-CD19 CAR T cells. As applicable, lymphocyte and monocyte populations residing in the CSF or other additional subject samples may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

Because axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored at baseline (prior to infusion) and at Month 3, Month 6, and Month 12 after axicabtagene ciloleucel infusion. In the LTFU, samples will continue to be collected yearly and may be held for up to 15 years from the last subject treated with axicabtagene ciloleucel. Additional testing will be conducted if a sample is positive at baseline, Month 3, Month 6, or Month 12 or as clinically indicated.

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, qPCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related DNA, RNA, or protein markers.

Archived tumor tissue (from most recent biopsy available) will be collected for centralized confirmatory diagnosis, evaluation of prognostic markers specific for iNHL, and pertaining to the tumor immune environment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged. Additional analysis may include CD19 expression, gene expression profiling, and analysis of somatic DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations) and tumor/immune-related RNA and protein markers.

For subjects who sign the optional portion of the consent form, on-study paired core biopsies of tumor will be performed at baseline (prior to conditioning chemotherapy) and between Day 7 and Day 14, following axicabtagene ciloleucel infusion, when peak expansion and tumor infiltration with anti-CD19 CAR T cells is expected. In addition, persisting, relapsing, or emerging lesions should also be biopsied to help determine eligibility for retreatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to axicabtagene ciloleucel or disease prognosis will be executed.

These samples, and any other components from these samples, may be stored up to 15 years from the last subject treated with axicabtagene ciloleucel to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the 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.

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.

7.11. Description of Study Periods

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 why the subject failed screening.

7.11.1. Screening

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment. Informed consent must be obtained before completion of any 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 (refer to Table 3 and Table 4).

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis 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 in the electronic CRF system with the reasons for failing screening.

In general, if a subject is screened and enrolled in the study, subjects must continue to meet all study inclusion and exclusion criteria at the time of administration of conditioning chemotherapy and at the time of axicabtagene ciloleucel infusion unless discussed in advance with and approved by the Kite medical monitor.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Medical history
- Physical exam, including neurological exam, height, and weight
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
  - Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of cerebral spinal fluid
- ECOG performance status
- ECG
- ECHO
- Imaging studies
  - Baseline PET-CT of the neck, chest, abdomen, and pelvis
    - PET-CT performed following the subject's last line of therapy and prior to signing the consent may be used for confirmation of eligibility, provided that the scan was obtained < 28 days before the initiation of conditioning chemotherapy.
    - If PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any anticancer therapy with therapeutic intent (eg, radiation, supraphysiologic doses of steroids, chemotherapy) between the last PET-CT and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET-CT should be performed as close to enrollment as possible.
- Bone marrow aspirate and biopsy as needed if not done previously
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel
  - CBC with differential
  - For EU sites, viral serologic tests (eg, HIV, Hep B, Hep C) will be carried out per institution guidelines and EU regulations. This may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

- SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- After eligibility is confirmed, submission of archival tumor tissue to the central lab and collection fresh tumor (for subjects who signed the optional portion of the consent)

7.11.2. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period may be permitted to rescreen. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the initial informed consent, only the procedures/assessments that did not originally meet the eligibility criteria need to be repeated. All other initial screening procedures/assessments do not need to be repeated.

If rescreening occurs or leukapheresis is delayed more than 28 days from the initial informed consent date, subjects must be re-consented and repeat all screening procedures/assessments. A subject will not be considered a screen failure until it is confirmed that the subject did not meet the eligibility criteria (ie, will not move forward to leukapheresis) and is no longer eligible for rescreening.

7.11.3. Enrollment/Leukapheresis

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

Additionally, the investigator must review the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis to confirm that Inclusion 112 (eg, creatinine clearance, serum ALT/AST, total bilirubin) continues to be met (see Section 5.1).

Before leukapheresis commences, the below criteria must be met. If criteria are not met, leukapheresis must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, baseline CBC with differential and chemistry panel must be repeated. If results are outside the eligibility criteria listed in Section 5, contact the Kite medical monitor prior to proceeding with leukapheresis.

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

If leukapheresis is delayed beyond 28 days from the screening visit, screening procedures will be repeated to confirm that the subject remains eligible for enrollment (see Section 7.11.1).

Leukapheresis should occur within approximately 5 days from eligibility confirmation.

After a subject commences leukapheresis, the subject will be considered enrolled into the study.

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA (refer to Table 3 and Table 4):

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of, or day before leukapheresis)
  - Chemistry panel
  - CRP, FER
  - CBC with differential
  - Blood draw for PBMCs (includes lymphocyte subsets and baseline RCR), cytokines, and antibodies to axicabtagene ciloleucel
  - Blood draw for leukapheresis
- AE/SAE reporting
- Concomitant medications documentation

7.11.4. Conditioning Chemotherapy and Axicabtagene Ciloleucel Infusion

Administration of CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion.

Signs, symptoms, or abnormal laboratory results attributed to the malignancy (eg “tumor fever,” elevated CRP) are diagnoses of exclusion that require a documented workup to establish.

Conditioning chemotherapy and axicabtagene ciloleucel infusion should only be initiated when it is reasonably assured that cell infusion can safely proceed.

Refer to Section 7.11.4.1 for workup requirements for potential infectious and/or inflammatory states.

7.11.4.1. Requirement to Workup Potential Infections and/or Inflammatory States

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

- Call Kite medical monitor
- Infectious disease service consult (if applicable)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic; x2 bottles each) and uric acid (UA) and urine culture. Deep/induced sputum culture if clinically indicated.
  - All indwelling lines such as central venous catheters should be examined for any signs of infection and additional cultures should be drawn from the line
  - Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a CNS process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral polymerase chain reaction (PCR) should be performed
- Any additional sign- or symptom-directed investigation should be performed as clinically indicated

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

If the axicabtagene ciloleucel infusion is delayed > 2 weeks following conditioning chemotherapy, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

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

7.11.5. Conditioning Chemotherapy Period

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, the workup listed in Section 7.11.4.1 must be performed to determine the potential cause if there is no identified source of infection.

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

Additionally:

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

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

The following procedures will be completed during Day –5 to Day –1 at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs (to be drawn prior to chemotherapy)
  - Chemistry panel
  - CBC with differential
- Fludarabine and cyclophosphamide administration
- AE/SAE reporting
- Concomitant medications documentation

7.11.6. Investigational Product Treatment Period

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the workup listed in Section 7.11.4.1 must be performed to determine the potential cause if there is no identified source of infection.

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

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam, including HEENT, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.

- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel (prophylactic use of antimicrobials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease service 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 infectious disease service consult (if applicable).

- Most recently collected blood, urine, or other body fluid cultures must show no growth for at least 48 hours, and any other infectious workup performed (eg, bacterial or viral serologies, PCR, stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

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

If the axicabtagene ciloleucel infusion is delayed > 2 weeks, protocol guidelines should be followed regarding the need for repeat conditioning chemotherapy.

Subjects will remain in the hospital through at least Day 7 following treatment with axicabtagene ciloleucel (please also refer to Section 18.2 for France). Subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities return to Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or slowly improving toxicities (eg, renal insufficiency), even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1 or if deemed necessary by the treating investigator.

Given the possibility that a subject could develop CRS or neurological event in the outpatient setting after discharge, subjects and their family members/caregivers should be educated on potential symptoms of these syndromes, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. If subjects develop these symptoms, they should be instructed to immediately contact the investigator or seek immediate medical attention.

During this period, the following procedures will be completed at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Daily physical and neurological exams are at the discretion of the investigator during hospitalization unless required by local ethics committees or regulatory agencies.

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature, every 4 to 6 hours during hospitalization

- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
  - Chemistry panel
  - CBC with differential (if WBCs are adequate per the local lab)
- Blood draw for PBMCs (includes lymphocyte subsets and anti-CD19 CAR T cells) and cytokines
- Infusion of axicabtagene ciloleucel
- As applicable, lumbar puncture for subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion.
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (any time between Day +7 and Day +14)
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, FER, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regard to CRS/neurological event. It is, therefore, recommended that CRP, FER, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continued through hospitalization. In addition, lactate should be monitored as clinically indicated.

7.11.7. Post-treatment Assessment Period

After completing axicabtagene ciloleucel infusion and discharged from the hospital, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (axicabtagene ciloleucel infusion), subjects will return to the clinic at the following intervals.

- Week 2 (± 2 days)
- Week 4 (± 3 days)
- Month 2 (± 1 week)
- Month 3 (± 1 week)

Subjects will allow key sponsor contacts to continue to access medical records so that information related to a subject's health condition and initial treatment response may be obtained. The following procedures will be completed for subjects as outlined in the SOA (refer to Table 3 and Table 4):

- Physical exam, including neurological exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature

- Disease assessment per the SOA (Note: If the PET-CT is not of high enough resolution to accurately quantify lesion size, the scan must be repeated.)
- As applicable, bone marrow aspirate and biopsy to confirm response (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)
- Labs
  - β-HCG pregnancy test (serum or urine) on all women of childbearing potential
  - Chemistry panel
  - CBC with differential
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis), cytokines, and anti-axicabtagene ciloleucel antibodies
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related AEs, the following procedures will be performed as outlined in the SOA (refer to Table 3 and Table 4):

- The labs below will be collected on the day of hospital re-admission and then weekly through the date of hospital discharge.
  - Blood draw for PBMCs (anti-CD19 CAR T cells)
  - Blood draw for cytokines
- If the subject has a new or ongoing Grade 3 or higher neurologic event, in addition to the labs above, blood draw for cytokines will be collected every other day through the date of hospital discharge.

At any time during the post-treatment assessment period, if a subject did not respond to treatment (ie, did not achieve a CR or partial response [PR]) or progresses following a response and is either not eligible for retreatment or chooses not to pursue retreatment, the subject will proceed directly to the Month 3 visit and be followed for **s**afety**,** survival, subsequent therapy, and disease outcomes in the LTFU period. A PBMC sample (for anti-CD19 CAR T cells, RCR) and tumor biopsy (for exploratory biomarker analysis) should be collected at the time of progression and prior to starting any subsequent anticancer therapy.

7.11.8. Long-term Follow-up Period

All enrolled subjects will be followed in the LTFU period for safety, survival, and disease status, if applicable. Subjects will begin the LTFU period after they have completed the Month 3 visit following axicabtagene ciloleucel infusion (whether they have responded to treatment or they went straight to the Month 3 visit due to disease progression), and will transition to the LTFU study after providing signed informed consent.

- Month 6 (± 2 weeks)
- Month 9 **(**+ 1 month)
- Month 12 (+ 1 month)
- Month 15 (± 2 weeks)
- Month 18 (± 2 weeks)
- Every 6 months (± 1 month) between Month 24 to Month 60
- If not already transitioned to the LTFU study, every 12 months (± 1 month) from Month 72 to Year 15

The following procedures will be completed for subjects who are enrolled and receive axicabtagene ciloleucel at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Physical exam, including neurological exam, through Month 24
- Disease assessment per the SOA. Diagnostic PET-CT may be used to document disease recurrence or progression if suspected.
- Survival status
- Labs
  - CBC with differential through Month 24
  - Blood draw for PBMCs (includes lymphocyte subsets, anti-CD19 CAR T cells, and RCR analysis) and anti-axicabtagene ciloleucel antibodies (refer to Section 7.9)
- Targeted AE/SAE reporting - (refer to Section 9 for safety reporting guidelines)
- Targeted concomitant medications documentation (for 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever comes first)
  - Including gammaglobulin, immunosuppressive drugs, anti-infective medications, and vaccinations
- Subsequent therapy for the treatment of lymphoma

Subjects may also be contacted by telephone to confirm survival status and report targeted concomitant medications use.

If a subject progresses in the LTFU phase, the subject will continue to be followed for survival status**,** any secondary malignancies**,** and subsequent therapy for the treatment of NHL. A PBMC sample (for anti-CD19 CAR T cells) and tumor biopsy (for exploratory biomarker analysis) should be collected at the time of progression and prior to starting any subsequent anticancer therapy. Also, if a subject develops a secondary malignancy during the study, every effort will be made to assay for RCR in blood and in a biopsy sample of the neoplastic tissue as clinically indicated (refer to Section 6.4.2.1 of the IB for additional details on the sponsor's testing procedure). Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

Subjects who are enrolled/leukapheresed, but did not receive axicabtagene ciloleucel treatment, will be followed only until the end of this study and will undergo the following procedures/assessments at the time points outlined in the SOA (refer to Table 3 and Table 4):

- Subsequent therapy
- Survival status–subjects may be contacted by telephone to confirm survival status
- Disease assessment per standard of care
- AE/SAE reporting and concomitant medications documentation until 30 days after last procedure (eg, leukapheresis, conditioning chemotherapy)

Should the subject fail to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, the subject will be considered lost to follow-up, and no additional contact will be required.

Subjects who undergo a consolidation SCT will be contacted to confirm the status of their disease, survival status, and will have blood collected for PBMCs per the LTFU schedule.

7.11.9. Retreatment

Subjects who achieve a response of PR or better at the 3-month disease assessment, but subsequently experience disease progression, may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel.

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

- Subject has at least PR or CR at the Month 3 disease assessment, but subsequently experienced progression of disease at a later time.

- CD19 expression on tumor cells confirmed locally by biopsy after disease progression and prior to treatment

- Subject continues to meet the original study eligibility criteria with the 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 lymphoma.

- Subject did not experience Grade 4 CRS, Grade 4 neurological event, or any other life-threatening toxicity during the original course of treatment.

- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment.

- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing KTE-C19 antibody develops, subject may be retreated if he or she meets the original study eligibility criteria).

Retreatment for all eligible subjects must occur within 24 months after the initial axicabtagene ciloleucel infusion. The decision to retreat with axicabtagene ciloleucel should be made in consultation with the Kite medical monitor. In addition, a discussion regarding benefits and risks of retreatment, including the need to undergo leukapheresis a second time for the manufacturing of axicabtagene ciloleucel, should occur with the subject prior to performing any study-related procedures or treatment. This conversation should also be recorded in the subject's source document.Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric {Lee 2015} and Surgery Branch {Kochenderfer 2015} of the NCI where 6 subjects in total have been retreated upon progression. Three (3) of the retreated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.

A maximum of 1 retreatment course may occur per subject.

Retreated subjects will remain on this study, following the same treatment schedule and procedural requirements per the initial treatment, until they are eligible to transfer to the LTFU study (please refer to Section 3.6).

Table 3. Schedule of Assessments (1 of 2)

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period					IP Administration Period		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**		**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7[11]**	**Week 2 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Medical history	X												
Physical exam (with neurological exam)	X							X	X[12]	X	X	X	X
Weight (plus height at screening)	X	X											
Vital signs (BP, HR, O_2 sat, temp)	X	X	X	X	X			X	X	X	X	X	X
Lumbar Puncture[1]	X								X				
ECOG Performance Status	X												
ECG	X												
ECHO	X												
Disease assessment (PET and/or CT, bone marrow **aspirate and** biopsy)[2]	PET-CT										PET-CT		PET-CT
Archival/Fresh tumor to central lab[3,4]	X								between Day 7 & Day 14				
Pregnancy test (serum or urine)	X												X
Viral serologic tests (except for US sites)[10]	X												
Blood draw for chemistry panel[9]	X	X	X	X	X			X	X	X	X	X	X
Blood draw for CBC w/differential	X	X	X	X	X			X	X	X	X	X	X
Blood draw for CRP, Ferritin		X											

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy Period					IP Administration Period		Post-treatment Follow-up (each visit calculated from Day 0)			
Day	**Within 28 days of enrollment**		**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1 – 7[11]**	**Week 2 (± 2 days)**	**Week 4 (± 3 days)**	**Month 2 (± 1 week)**	**Month 3 (± 1 week)**
Blood draw for anti-KTE-C19 antibody[5]		X									X		X
Blood draw for PBMCs[6,7]		X							Day 7[7]	X	X		X
Blood draw for cytokines[7,8]		X						X	Day 3,7[7]	X	X		
Leukapheresis		X											
Fludarabine/Cyclophosphamide			X	X	X								
KTE-C19 infusion IV								X					
Adverse events/Concomitant medication	X	→											

Abbreviations: BP, blood pressure; HR, heart rate; sat, saturation; temp, temperature; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; PET, positron emission tomography; CT, computed tomography; CBC, complete blood count; CRP, C-reactive protein; PBMC, peripheral blood mononuclear cell; IV, intravenous; IP, investigational product.

1 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 post-axicabtagene ciloleucel infusion will have lumbar puncture performed to assess CSF. Opening pressures for all lumbar punctures (LPs) should be measured and recorded whenever possible.

2 PET and/or CT (neck-chest-abdomen-pelvis)/disease assessment: All scans will be submitted to the central imaging vendor to be read by a central independent reviewer. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy, the baseline PET-CT scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. PET-CT will be performed at the Week 4, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, and Month 24 visits and at any subsequent scheduled or unscheduled visit if there is clinical concern for disease progression. After Month 24, PET-CT will be performed if disease recurrence is suspected. Otherwise, surveillance imaging will be diagnostic CT without PET**.** A bone marrow aspirate and biopsy will be required to confirm a complete response to axicabtagene ciloleucel except among subjects known to be negative for bone marrow involvement within 4 weeks of screening. As applicable, bone marrow aspirate and biopsy will be performed if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. See Section 7.9 and Section 7.11.

3 For archival tumor samples, either formalin-fixed paraffin embedded (FFPE) tumor block or 20 unstained slides is accepted. If not able to send a FFPE block or at least 20 unstained slides, refer to the central lab manual for further instruction. Site must attempt to ship archived tumor samples to the central laboratory after eligibility has been confirmed and prior to the start of conditioning chemotherapy. Fresh tumor sample for subjects who sign the optional portion of consent (refer to Section 7.10) will be collected and shipped after eligibility has been confirmed and prior to the start of conditioning chemotherapy. Post-treatment fresh tumor samples (if applicable) will be collected/submitted any time between Day 7 and Day 14. See Section 7.10.

4 Archived tumor tissue will be collected for central confirmatory diagnosis, central pathology review, and evaluation of prognostic markers specific for iNHL and pertaining to the tumor immune microenvironment. If an archival sample is not available, a fresh biopsy sample collection is strongly encouraged.
5 Blood draw for anti-axicabtagene ciloleucel antibody: Baseline antibody sample to be collected prior to start of conditioning chemotherapy and a post-axicabtagene ciloleucel infusion sample will be collected at the Month 3 visit; see Section 7.9.
6 PBMCs blood draw for the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR. See Section 7.10. Day 7 blood draws for PBMCs that fall on a weekend or public holiday may be drawn on Day 6 or Day 8 (Day 5 only if Day 6 or Day 8 cannot be done).
7 If, following discharge from initial hospitalization, the subject is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related adverse events, blood samples for PBMCs (anti-CD19 CAR T cells) and cytokines will be collected on day of admission, then weekly while hospitalized, and on the day of discharge. If the subject has a new or ongoing Grade 3 or higher neurological event, blood samples for cytokines will be collected every other day while hospitalized, and on the day of discharge.
8 A blood draw for cytokines will be drawn at Day 3 and Day 7. Day 3 blood draws for cytokines that fall on a weekend or public holiday may be drawn on Day 2 or Day 4 (Day 1 only if Day 2 or Day 4 cannot be done). Day 7 blood draws for cytokines that fall on a weekend or public holiday may be drawn on Day 6 or Day 8 (Day 5 only if Day 6 or Day 8 cannot be done). If the subject experiences Grade 3 axicabtagene ciloleucel-related toxicity, such as Grade 3 CRS or neurological event, one additional blood draw for cytokines will be taken at the time of Grade 3 related toxicity.
9 Urea is an acceptable alternative if BUN cannot be analyzed by the local lab.
10 Except for US sites, viral serologic tests will be done at screening or at the time of leukapheresis or within the 30 days prior to leukapheresis (see Section 7.9.1).
11 Subjects will remain in the hospital through Day 7 after treatment with axicabtagene ciloleucel unless otherwise required by country regulatory agencies (see Section 18.2)
12 Daily physical and neurological exams are at the discretion of the investigator during hospitalization unless required by local ethics committees or regulatory agencies.

Table 4. Schedule of Assessments (2 of 2)

Procedure	LTFU Period[1] (Each visit calculated from Day 0)												
Visit Frequency	**Month 6**	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 24**	**Month 30**	**Month 36**	**Month 42**	**Month 48**	**Month 54**	**Month 60**	**Month 72 and Annually Until Year 15**
	(± 2 weeks)	**(+ 1 month)**	**(+ 1 month)**	**(± 2 weeks)**	**(± 2 weeks)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**	**(± 1 month)**
Physical exam (with neurological exam)[2]	X	X	X	X	X	X							
PET/CT disease assessment[3]	PET-CT	PET-CT	PET-CT	PET-CT	PET-CT	PET-CT		CT[3]		CT[3]		CT[3]	CT[3]
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential[4]	X	X	X	X	X	X							
Anti-KTE-C19 antibody[5]													
Blood draw for PBMCs[6]	X		X		X	X		X		X		X	X[5]
Targeted AE/SAEs related to axicabtagene ciloleucel infusion[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted concomitant medication[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Subsequent therapy for NHL[9]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: LTFU, long-term follow-up; PET, positron emission tomography; CT, computed tomography; CBC, complete blood count; PBMC, peripheral blood mononuclear cell; AE, adverse event; SAE, serious adverse event; NHL, non-Hodgkin lymphoma.

1 After completing at least 60 months (FL subjects) or at least 24 months (MZL subjects) of assessments in this study since the initial axicabtagene ciloleucel infusion and after agreement by the Sponsor, subjects will complete the remainder of the 15 year follow-up assessments in a separate Kite Pharma, Inc-sponsored long-term follow-up (LTFU) study, KT-US-982-5968.

2 Physical exams (including neurological exam) will continue through the first 24 months.

3 The Month 9 and Month 12 PET/CT disease assessment should occur at the Month 9 + 1 month and Month 12 + 1 month, respectively. PET-CT scans/disease assessments will continue every 3 months through Month 18 and at Month 24 or until disease progression, whichever comes first. After Month 24, PET-CT will be performed if disease recurrence is suspected. Otherwise, surveillance imaging will be diagnostic CT without PET.

4 Subjects will continue to provide samples for CBC w/differentials and lymphocyte subsets through Month 24.

5 Anti-axicabtagene ciloleucel antibodies post-3-month samples; refer to Section 7.9.

6 Blood draw for PBMCs includes the analysis of lymphocytes, anti-CD19 CAR T cells, and RCR. RCR will be tested at baseline, Month 3, Month 6 and Month 12. In the LTFU, samples will be collected yearly and may be held for up to 15 years from the last subject treated with axicabtagene ciloleucel.

7 Targeted AEs and SAEs related to axicabtagene ciloleucel infusion will be collected for 15 years, until disease progression, or until initiation of subsequent anticancer therapy (whichever occurs first).. All new malignancies are to be reported for all subjects through 15 years after initial axicabtagene ciloleucel infusion, including those whose disease progresses and/or those who receive subsequent anticancer therapy.
8 Targeted concomitant medications will be collected for 24 months after axicabtagene ciloleucel infusion or until disease progression (whichever occurs first).
9 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 LTFU period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for iNHL and to assess survival status.

8. SUBJECT WITHDRAWAL

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

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

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

Withdrawal of full consent for a study means that the subject does not wish to receive further protocol-required therapy or undergo procedures and the subject does not wish to continue further study follow-up. 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 (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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

8.1. Reasons for Removal from Treatment

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

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

8.2. Reasons for Removal from Study

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

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

9. SAFETY REPORTING

9.1. 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 includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

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

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

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

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. In the event a subject requests to withdraw from protocol-required therapies or the study due to an AE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA (refer to Table 3 and Table 4).

9.2. Reporting of AEs

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from enrollment (ie, commencement of leukapheresis) through 3 months after treatment with axicabtagene ciloleucel infusion or until the initiation of another anticancer therapy, whichever occurs first. After 3 months, targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) related to axicabtagene ciloleucel infusion will be monitored and reported for 15 years after initial treatment with axicabtagene ciloleucel, until disease progression, or the initiation of subsequent anticancer therapy, whichever occurs first.

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

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

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

AE grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the axicabtagene ciloleucel IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) the IP (axicabtagene ciloleucel), 2) conditioning chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

The investigator is 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, require therapy, or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

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

- 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
- Clinically significant in the investigator's judgment

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

9.3. Definition of SAEs

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

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

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

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

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

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

9.4. Reporting of SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the screening informed consent through 3 months after the axicabtagene ciloleucel infusion, until disease progression, or until the initiation of subsequent anticancer therapy, whichever comes first. After 3 months, only serious targeted AEs (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) related to axicabtagene ciloleucel infusion are to be reported for 15 years after initial axicabtagene ciloleucel infusion, until disease progression, or until the initiation of subsequent

anticancer therapy, whichever occurs first. All new malignancies are to be reported for all subjects through 15 years, including those whose disease progresses and/or those who receive subsequent anticancer therapy. New malignancies are defined as the development of any new malignancies occurring after axicabtagene ciloleucel infusion. Secondary malignancies are defined as new malignancies that are suspected to be possibly related to axicabtagene ciloleucel (ie, plausibly associated with axicabtagene ciloleucel and without compelling alternate etiologies).

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

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

All SAEs must be reported within 24 hours of the investigator's knowledge of the event. SAEs will be reported through the electronic database capture (EDC) system. This is called eSAE reporting. If the eSAE system is unavailable, reports will be submitted by emailing a completed SAE report form to PPD .

After completion of ZUMA-5 study and database closure, any relevant information on ongoing SAEs must be submitted to Kite within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via email to the SAE Reporting mailbox: PPD .

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

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and being indicated as due to disease progression. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or axicabtagene ciloleucel, then the event malignant neoplasm progression must be recorded as an SAE with the outcome fatal.

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

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

9.4.1. Reporting Deaths

Deaths occurring during the protocol-specified AE reporting period that investigators attribute solely to progression of underlying lymphoma should be recorded as SAEs and on the AE electronic CRF with the preferred term "Follicular Lymphoma, Marginal Zone Lymphoma, or B-cell lymphoma" and must be reported to the sponsor immediately. Death is an outcome and not a distinct event. For deaths not due to the underlying malignancy, the event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later (eg, after autopsy). Deaths occurring during the post-study survival follow-up period that are due to underlying cancer should be recorded on the Survival Status CRF and the Death Summary Page.

9.5. Diagnosis Versus Signs and Symptoms

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

9.6. Pregnancy and Lactation

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

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 12 months after administration of conditioning chemotherapy or 12 months after axicabtagene ciloleucel dosing, whichever is longer. Male subjects are recommended to not father a child for 12 months after conditioning chemotherapy or 12 months after axicabtagene ciloleucel dosing, whichever is longer. If a pregnancy occurs in a female subject enrolled into the study at any time after infusion or a female partner of a male subject within 12 months of completing conditioning chemotherapy or axicabtagene ciloleucel infusion, whichever is longer, the pregnancy must be reported to the key sponsor contact. Pregnancies should be reported within 24 hours of the investigator's knowledge of the pregnancy event. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

If a lactation case occurs while the female subject is taking protocol-required therapies, report the lactation case to the key sponsor contact. Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 12 months.

9.7. Hospitalization and Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE, as described in Section 9.3.

The following hospitalization scenarios are not considered to be SAEs:

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

9.8. Abnormal Vital Sign Value

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

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

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised when deciding whether 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 on the CRF.

9.9. DSMB

An independent DSMB will have ongoing oversight of the study and will monitor data during this study. The DSMB will first meet to review safety data when 10 subjects have been treated with axicabtagene ciloleucel (see Section 10.5) and have had an opportunity to be followed for 4 weeks. The DSMB will meet again to review safety data after 30 subjects have been treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. The DSMB will meet again to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB

will meet for a fourth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. The DSMB will meet for a fifth time when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease response assessment.

The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed. The DSMB can make a recommendation to the sponsor to discontinue the study early based on the guidelines in the DSMB charter.

The DSMB will also review SAE information and SUSARs on a regular basis throughout subject treatment in the study. The DSMB may request additional safety data or modify the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate and ensure timely DSMB review.

At the time of expedited reporting of SUSARs to regulatory authorities, Kite (or designee) will concurrently submit these reports to the DSMB chair. The DSMB chair will also review SAE narrative reports monthly. Finally, the DSMB or Kite may request additional analyses of safety data if a safety concern arises during the course of the trial.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

Four hypotheses will be tested using a fixed sequence procedure in terms of ORR and CR rate as determined by central review to control the overall type I error at 1-sided alpha level of 0.025 with the following testing order:

- Hypothesis 1 (H_1): test for ORR, as determined by central review; if significant then
- Hypothesis 2 (H_2): test for CR rate, as determined by central review; if significant then
- Hypothesis 3 (H_3): test for ORR, as determined by central review, in the subjects who have had 3 or more lines of prior therapy; if significant then
- Hypothesis 4 (H_4): test for CR rate, as determined by central review, in the subjects who have had 3 or more lines of prior therapy

The hypotheses H_1 through H_4 will be assessed at the time of the interim analysis 3**,** 4, and 5 and the primary analysis.

The H_1 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set. The targeted response rate is 60%.

The H_2 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL in the inferential analysis set.

The H_3 is that the ORR, as determined by central review, to axicabtagene ciloleucel is significantly greater than 40% in subjects with FL in the inferential analysis set who have had 3 or more lines of prior therapy.

The H_4 is that the CR rate, as determined by central review, to axicabtagene ciloleucel is significantly greater than 15% in subjects with FL in the inferential analysis set who have had 3 or more lines of prior therapy.

An alpha spending function will be used to allocate the alpha level between the interim analysis 3, interim analysis 4, and interim analysis 5, and the primary analysis. Using the O'Brien-Fleming boundary of the Lan-DeMets family of alpha spending functions, the nominal 1-sided alpha used to test for efficacy at interim analysis 3, interim analysis 4, and interim analysis 5 are 0.0003, 0.0005, and 0.0005, respectively, and the nominal 1-sided alpha used to test for efficacy at the primary analysis is 0.0237. If the criteria for early efficacy are met for H_1, the same alpha spending function will be applied to test H_2 at each interim analysis; otherwise, H_2 through H_4 will not be tested until the primary analysis. If the criteria for early efficacy are met for H_1 and H_2, the same alpha spending function will be applied to test H_3; otherwise, H_3 and H_4 will not be

tested until the primary analysis. If the criteria for early efficacy are met for H_1, H_2, and H_3, the same alpha spending function will be applied to test H_4; otherwise, H_4 will not be tested until the primary analysis. The study will not be stopped if early efficacy is demonstrated.

No formal hypothesis testing is planned for the MZL histological subtype. The analyses will be descriptive.

10.2. Study Endpoints

10.2.1. Primary

ORR is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the central reader. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered nonresponders.

10.2.2. Secondary

The CR rate is defined as the incidence of CR as best response to treatment by the Lugano Classification {Cheson 2014} as determined by the central reader.

ORR is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the central reader for those subjects who have had 3 or more lines of prior therapy.

The CR rate is defined as the incidence of CR as best response to treatment by the Lugano Classification {Cheson 2014} as determined by the central reader for those subjects who have had 3 or more lines of prior therapy.

ORR per investigator read is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by the investigator. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered nonresponders.

Best objective response is defined as the incidence of CR, PR, stable disease (SD), PD, or non-evaluable (NE) as best response to treatment by the Lugano Classification {Cheson 2014}. Response may be defined per central read or investigator read.

DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression per {Cheson 2014} or death due to any cause. Response and progression may be defined per central read or investigator read. Subjects not meeting the criteria for progression or death due to any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive any subsequent anticancer therapy (including SCT or retreatment with axicabtagene ciloleucel) in the absence of prior documented progression will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy. The DOR for subjects who progress or die after any subsequent anticancer therapy, including SCT or retreatment with axicabtagene ciloleucel, will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy.

PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per {Cheson 2014}or death due to any cause. Subjects not meeting the criteria for progression or death due to any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive any subsequent anticancer therapy (including SCT or retreatment with axicabtagene ciloleucel) in the absence of prior documented progression will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy. The PFS for subjects who progress or die after any subsequent anticancer therapy, including SCT or retreatment with axicabtagene ciloleucel, will be censored at the last evaluable disease assessment prior to the subsequent anticancer therapy.

OS is defined as the time from axicabtagene ciloleucel infusion to the date of death due to any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date. Survival for subjects known to be alive or determined to have died after the data cutoff date will be censored at the data cutoff date.

Other secondary endpoints are as follows:

- Incidence of AEs and clinically significant changes in laboratory values
- Incidence of anti-axicabtagene ciloleucel antibodies
- Levels of anti-CD19 CAR T cells in blood
- Levels of cytokines in serum
- Time to next therapy: defined as the time from the axicabtagene ciloleucel infusion date to the start of the subsequent new lymphoma therapy or death from any cause. Subjects who have not received subsequent new therapy and are still alive will be censored at the last contact date.

10.2.3. Covariates

The following covariates may be used in efficacy and safety analyses

- Age ($< 65, \geq 65$ years)
- Gender
- Race
- Ethnicity
- Histological diagnosis (eg, FL, MZL), by both local and central pathology
- FLIPI (age > 60, Hgb < 12, Stage 3 or 4, > 4 nodal sites, elevated LDH)

- ECOG status (0 vs 1)
- Disease burden as defined by any of the following GELF criteria (subject meets the criteria for high tumor bulk versus subject does not meet the criteria for high tumor bulk)
  - Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
  - Any nodal or extra-nodal tumor mass with a diameter of ≥ 7 cm
  - B symptoms
  - Splenomegaly
- Relapsed vs refractory status at study entry
- Time to relapse from initiation of first anti-CD20-chemotherapy combination therapy (≥ 24 months, < 24 months)
- Prior PI3K inhibitor
- Number of prior lines of therapy (excluding single agent anti-CD20 antibody as a line of therapy)
- Double refractory (subjects refractory to the first 2 lines of therapy)

10.3. Sample Size Considerations

The trial uses a single-arm design to estimate the ORR in subjects with r/r B-cell iNHL treated with axicabtagene ciloleucel. The target response rate in subjects with FL is 60%.

Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, will be enrolled and treated.

The primary efficacy endpoint for this study in at least 80 subjects with FL in the inferential analysis set has 93% power to test the null hypothesis that the ORR is 40% versus the alternative hypothesis that the ORR is 60% with a 1-sided alpha level of 0.0237.

Within the inferential analysis set, interim analysis 3, 4, and 5 will be performed when 30 subjects with FL have had the opportunity to be followed for response for 6 months after axicabtagene ciloleucel infusion, when 80 subjects with FL have had the opportunity to be followed for response for 6 months after axicabtagene ciloleucel infusion, and when 80 subjects with FL have had the opportunity to be followed for response 9 months after the first disease response assessment. These interim analyses will be for safety and to assess early demonstration of efficacy. The interim analyses are based on the interpolated alpha spending function. The nominal alpha levels for the assessment of efficacy are 0.0003, 0.0005, and 0.0005. The study will not be stopped if early efficacy is demonstrated and the primary analysis will occur after at least 80 subjects with FL in the inferential analysis set and have had the opportunity to be followed for 12 months after the first disease response assessment.

10.4. Statistical Assumptions

Treatment outcomes for subjects with r/r iNHL who have had > 2 prior regimens are exemplified by the clinical trials of the PI3K-inhibitors, idelalisib (Zydelig®) {Gopal 2014}, and copanlisib (Aliqopa) {Dreyling 2017}. In these trials, the ORRs were 57% and 59%, respectively, with CR rates of 6% and 12%, respectively. See Section 2.

In the current trial, it is anticipated that most subjects will have had prior treatment with at least one of these agents; thus, an ORR < 40% or CR < 15% would not be of clinical interest.

10.5. Analysis Subsets

The following analysis sets are defined:

The pivotal cohort is defined by the eligibility criteria specified below:

1) Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal or extranodal, based on criteria established by the WHO 2016 classification

2) Relapsed or refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. (Single agent anti-CD20 antibody will not count as a line of therapy for eligibility). Stable disease (without relapse) > 1 year from completion of last therapy is not eligible.

    a) The safety analysis set will consist of all subjects treated with any dose of axicabtagene ciloleucel.

    b) The inferential analysis set will consist of all enrolled subjects who meet the eligibility criteria for the pivotal cohort and were treated with any dose of axicabtagene ciloleucel. This analysis set will be used for all analyses of objective response and endpoints based on objective response (best overall response, DOR, PFS).

    c) The full analysis set (FAS) will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of ORR and PFS, and subject listings of deaths.

10.6. Access to Individual Subject Treatment Assignments

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

10.7. Interim Analysis

The DSMB will review safety data after 10 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks for safety. This analysis will be for safety only.

The DSMB will meet again to review safety data after 30 subjects in the safety analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 4 weeks. This analysis will be for safety only.

The DSMB will meet again to review safety and efficacy data after 30 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion. This analysis will be for safety and efficacy.

The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 6 months after axicabtagene ciloleucel infusion.

The DSMB will meet again to review the safety data when 80 subjects with FL in the inferential analysis set have been enrolled and treated with axicabtagene ciloleucel and have had an opportunity to be followed for 9 months from the first disease assessment date.

The DSMB will also review SAE information and SUSARs on a regular basis throughout the study. The sponsor may request additional reviews by the DSMB if safety concerns are identified. The DSMB may meet more often as needed.

10.8. Planned Methods of Analysis

The interim analysis 5 will be performed when at least 80 subjects with FL in the inferential analysis set have had the opportunity to be followed for 9 months after the first disease response assessment. The primary efficacy analysis of response rate will be performed when at least 80 subjects with FL in the inferential analysis set have had the opportunity to be followed for 12 months after the first disease response assessment. A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). The CSR will be written based on the data collected and analyzed from the primary analysis. Kite will ensure that the report meets the standards set out in the International Conference on Harmonisation (ICH) Guideline for Structure and Content of Clinical Study Reports (ICH E3). After the primary analysis, additional follow-up analyses of efficacy and safety will be performed as needed to satisfy regulatory requirements and to perform long-term efficacy, safety, and OS follow-up. The final analysis will occur when all subjects have completed the study.

The primary analysis for ORR as primary endpoint will be based on central review of disease assessments per the Lugano Classification {Cheson 2014}. The ORR based on investigator review of the disease assessment will be used as the sensitivity analysis for ORR.

Efficacy summaries will be presented by histological subtype (eg, FL and MZL) and overall.

10.8.1. ORR

The subject incidence of objective response will be calculated and 2-sided 95% confidence intervals will be calculated with the Clopper-Pearson method. An exact binomial test will be used to compare the ORR per central read among the subjects with FL and among the subjects with FL who have had 3 or more lines of prior therapy to the hypothesized historical control rate of 40%.

The incidence of subjects with CR, PR, SD, PD, and NE as best overall response to treatment and exact 2-sided 95% confidence intervals about the incidence will be generated.

10.8.2. CRR

The subject incidence of CR will be calculated. The 2-sided 95% confidence intervals will be provided about the CR rate, calculated with the Clopper-Pearson method. An exact binomial test will be used to compare the observed CR rate per central read among the subjects with FL and among the subjects with FL who have had 3 or more lines of prior therapy to the hypothesized historical control rate of 15% if ORR is statistically significant.

10.8.3. DOR

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for DOR. Kaplan-Meier estimates will be provided for the proportion of subjects who are alive and progression-free at 3-month time intervals. The number of subjects censored or having events will be summarized, as well as the reasons for censoring and the event type (PD or death). Analyses will be generated for DOR per central read and per investigator read. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

10.8.4. PFS

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

10.8.5. OS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for OS. Estimates of the proportion of subjects alive at 3-month, 6-month, and 12-month intervals will be provided.

10.8.6. Time to Next Therapy

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for time to next therapy.

10.8.7. Safety

Safety summaries will be provided by FL, MZL, and overall. AEs will be graded using the CTCAE version 4.03 or above. Subject incidence rates of all AEs, including serious AEs, fatal AEs, Grade 3 or higher AEs, and treatment -related AEs will be reported throughout the conduct of the study and will be tabulated by preferred terms and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medication use will be summarized.

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

10.8.8. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives his or her last axicabtagene ciloleucel infusion. LTFU data analysis will be performed on subjects in the study and after transition to the LTFU study. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10.8.9. Follow-up Analysis

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

11. REGULATORY OBLIGATIONS

11.1. IRB/IEC

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

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

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

11.2. Subject Confidentiality

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.

Kite has established processes in place to ensure the security and confidentiality of data records and personal information. This includes the following: restricting access, via secure login information for individual authorized users, to electronic personal data and study data systems; pseudonymization of study subject data; encryption of all personal data in transit and at rest; and a robust data privacy and security due diligence process with third party vendors, which includes a written contract with each vendor to abide by privacy and security obligations. Processes are also in place to avoid loss of information. Should a data security breach occur, Kite will follow its relevant standard operating procedures to mitigate the impact. Kite will abide by all available national and international data protection legislation. Further details on what personal data are collected, where they are stored, how they are processed and who will have access is described in the study country-specific patient information sheets.

The investigator agrees that all information received from Kite, including but not limited to the IB, this protocol, eCRFs, the study drug, site initiation visit presentation slides, 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.

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

- Subjects will be identified by a unique ID number
- Date of birth or year of birth/age at time of enrollment will be reported in accordance with local laws and regulations

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

Per regulations and International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) guidelines, investigators and institutions are required to permit authorization to the sponsor, contract research organization (CRO), IRB/IEC, and regulatory agencies to access subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes personal information.

11.3. Investigator Signatory Obligations

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

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

12. PROTOCOL AMENDMENTS AND TERMINATION

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

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 and provide the sponsor with a copy of the correspondence.

Kite reserves the unilateral right, at its sole discretion, to determine whether to manufacture axicabtagene ciloleucel T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

13. STUDY DOCUMENTATION AND ARCHIVE

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

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

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

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

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite and the investigator. 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 prior to the shipping the documents.

Traceability records for the product, from procurement through manufacture to the administration of the product, should be kept by each relevant party (eg, the sponsor and the 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 the sponsor. 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 product, while ensuring the data protection legally required for the subject.

If the investigator cannot provide 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 the 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 is transferred 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.

14. STUDY MONITORING AND DATA COLLECTION

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

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

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

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

All data will be collected in an electronic CRF system. All entries must be completed in English, and concomitant medications should be identified by trade names. For additional details surrounding the completion of CRFs, refer to the CRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-105 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

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

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

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

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

16. COMPENSATION

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

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18. APPENDICES

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18.1. Sponsor and Investigator Signature Page

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

STUDY ACKNOWLEDGMENT

A PHASE 2 MULTICENTER STUDY OF AXICABTAGENE CILOLEUCEL IN SUBJECTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA (INHL)

Amendment 8.0, 29 January 2024

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 the 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

18.2. Country-specific Regulatory Agency Requirements - France

The postinfusion monitoring of subjects in this protocol will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "IP Administration Period, D1 to 7". The L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) recommends a 10-day hospitalization after infusion of any CAR T-cell product.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with CRP (see Section 7.11.6), blood draw for CBC w/differential (see Section 7.9), and physical/neurological assessment. Any observed toxicity will be managed according to Section 6.5 of this protocol.

18.3. Lugano Classification

Refer to the imaging manual and {Cheson 2014} for details of assessment.

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

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

18.3.1. Complete Remission

18.3.1.1. Complete Metabolic Response (CMR) for Positron Emission Tomography-computed (PET-CT) Based Response

The designation of complete metabolic response (CMR) requires all of the following:

- A 5PS (5-point scale) score of 1, 2, or 3, with or without a residual mass
  - In Waldeyer's ring or extra-nodal sites with high physiologic uptake or with activation within spleen or marrow, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR 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

18.3.1.2. Complete Radiologic Response for CT-based Response

The designation of complete radiologic response (CRR) requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion (LDi)
- No extra-lymphatic sites of disease
- Absent non-measured lesion
- Organ enlargement regress to normal
- No new sites of disease should be observed.
- Bone marrow normal by morphology; if indeterminate, immunohistochemistry (IHC) negative

18.3.2. Partial Remission

18.3.2.1. Partial Metabolic Response for PET-CT-based Response

The designation of partial metabolic response (PMR) requires all of the following:

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

  Note:

  — At interim, these findings suggest responding disease.

  — At end of treatment (EOT), these findings suggest residual disease.

- No new sites of disease should be observed.

- Residual uptake higher than uptake in normal bone marrow, but reduced compared with baseline (diffuse uptake 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 (MRI) or biopsy or an interval scan.

18.3.2.2. Partial Radiologic Response for CT-based Response

The designation of partial radiologic response (PRR) requires all of the following:

- ≥ 50% decrease in sum of the product of the perpendicular diameters (SPD) of up to 6 target measurable nodes and extra-nodal sites.

  — When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value.

  — When no longer visible, 0 x 0 mm

  — For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation.

- Absent/normal, regressed, but no increase of non-measured lesions

- Spleen must have regressed by > 50% in length beyond normal.

- No new sites of disease should be observed.

18.3.3. Stable Disease

18.3.3.1. No Metabolic Response for PET-CT-based Response

The designation of no metabolic response (NMR) requires all of the following:

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

18.3.3.2. Stable Radiologic Disease for CT-based Response

The designation of stable radiologic disease (SRD) requires all of the following:

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

18.3.4. Progressive Disease

18.3.4.1. Progressive Metabolic Disease for PET-CT-based Response

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

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

18.3.4.2. Progressive Radiologic Disease for CT-based Response

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

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

18.4. Tabulated List of Investigational Medicinal Products and Auxiliary Medicinal Products for EU

A list of all investigational and auxiliary medicinal products which can be used in Protocol KTE-C19-105 is provided in Table 5 and Table 6 in compliance with EU Reg. 536/2014 Annex I Section D No. 17 lit. f. All the investigational and auxiliary medicinal products used in the clinical trial are authorized in the EU and are used in accordance with their authorized product information in any given country (eg, Package Insert, SmPC) and institutional guidelines.

Table 5 List of Investigational Medicinal Product

Investigational Medicinal Products	Further information on dosage, dose regimen, route of administration and treatment period
Axicabtagene ciloleucel	Please refer to Section 6.2.1 of the protocol

Table 6. List of Auxiliary Medicinal Products

AxMPs[a]	Further information on dosage, dose regimen, route of administration and treatment period
Acetaminophen (paracetamol) or equivalent	Please refer to Section 6.4.3.1 of the protocol
Diphenhydramine or equivalent	
Cyclophosphamide (as lymphodepleting chemotherapy)	Please refer to Sections 6.3.1 and 7.11.4.1 of the protocol.
Fludarabine (as lymphodepleting chemotherapy)	
Mesna	
Tocilizumab	These AxMPs are not all specified in the protocol, however, are suggested within the standard of care toxicity management guidelines referred to in Section 6.5 of the protocol and further discussed in Sections 6.5.1 and 6.5.2 of the IB
Dexamethasone (as toxicity management)	
Methylprednisolone	

Abbreviations: AxMP, auxiliary medicinal product; IB, Investigator's Brochure.
a All AxMPs listed have marketing authorization in all countries participating in ZUMA-5. No AxMP is classified as a narcotic, psychotropic, radiopharmaceutical, or orphan medicine.

18.5. Protocol Amendment History

High-level summaries of the history of this study's amendments are provided in tabular form in the subsections below (from the most recent amendment to the oldest), with changes listed in order of importance. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Earlier separate summaries of changes for previous amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 7 to this amendment (Amendment 8) will be made available.

18.5.1. Amendment 8 (29 January 2024)

Section Number and Name	High-level Description of Change	Brief Rationale
Synopsis and Section 10.2.3	One of the key covariates for ORR was changed from "Time to relapse from completion of first anti-CD20 chemotherapy" to "time to relapse from initiation of first anti-CD20 chemotherapy"	The change was made to address the discrepancy between the protocol and SAP Version 4.0.
Section 2.5	A benefit/risk assessment section was added in which a reference to the IB was made.	Benefit/risk assessment of axicabtagene ciloleucel was provided to align with the Clinical Trials Regulation (Regulation [EU] No 536/2014).
Sections 6.2.1, 6.2.2, and 18.4	• A description and a list of investigational and auxiliary medicinal products were added. To accommodate this change, the 'Axicabtagene Ciloleucel' section that was previously in Section 6.2.2 was moved to Section 6.2.1. • The approximate number of subjects who have received the various doses of axicabtagene ciloleucel in this study so far was removed. • Instructions for reporting of any problems related to the use of axicabtagene ciloleucel was revised.	• The additional information was added to provide a list of investigational and authorized auxiliary medicinal products used in the study and to align with the Clinical Trials Regulation (Regulation [EU] No 536/2014). • The information is not necessary to be presented in the protocol. • The revision was provided for clinical site staff to report any problems related to the use of axicabtagene cilolceucel according to the instructions in the IPM.

Section Number and Name	High-level Description of Change	Brief Rationale
Section 9.9	A sentence was added to reflect that the DSMB can make a recommendation to the sponsor to discontinue the study early based on the guidelines in the DSMB charter.	The added sentence was provided to align with the Clinical Trials Regulation (Regulation [EU] No 536/2014).
Section 11.2	Additional paragraphs regarding subject confidentiality were added.	The additional paragraphs were provided to align with the Clinical Trials Regulation (Regulation [EU] No 536/2014).

Abbreviations: DSMB, Data Safety Monitoring Board; EU, European Union; IB, Investigator's Brochure; IPM, Investigational Product Manual; ORR, objective response rate; SAP, statistical analysis plan.

18.5.2. Amendment 7 (22 February 2023)

Section Number and Name	High-level Description of Change	Brief Rationale
Synopsis, Study Schema, Sections 3.5, 3.6, 6.2.5, 7.11.8, 7.11.9, 10.8.8, Table 4	The timing of subject transition to a separate long-term follow-up protocol (KT-US-982-5968) was defined.	New guidance added to reference transition to the LTFU study.
Section 9.2, 9.4, Table 4	Timeline for reporting targeted AEs and SAEs was lengthened. Additionally, clarification was added that only targeted AEs and SAEs related to axicabtagene ciloleucel need to be reported from 3 months through 15 years, until disease progression, or until the initiation of subsequent anticancer therapy.	Timeline for reporting targeted AEs and SAEs was lengthened due to regulatory agency feedback. Clarification that only targeted AEs and SAEs need to be reported from 3 months to 15 years added due to regulatory agency feedback.
Section 7.11.8, Section 9.4	Updated definition of secondary malignancies	Clarification.
Section 9.4	Included details for SAE reporting after completion of study and database closure.	Clarification.
Section 6.2.5	Language added clarifying collection of anticancer therapy information for subjects who are enrolled but do not receive axicabtagene ciloleucel infusion.	Clarification.
Section 7.11.9	Retreatment limited to 24 months after initial axicabtagene ciloleucel infusion.	Retreatment limit added to align with other Kite studies.
Section 5.2, 9.6	Updated contraception language from 6 months to 12 months.	Contraception language updated due to regulatory agency feedback.

Section Number and Name	High-level Description of Change	Brief Rationale
Section 13	Study documentation and archive language updated.	Clarification.
Section 18.8	Pandemic Risk Assessment and Mitigation Plan Language added.	New section added to summarize potential risks associated with subjects being unable to attend study visits.
Section 6.4.3, 7.11.6, 18.2	Added country-specific regulatory agency requirements for post-infusion monitoring of subjects in France.	Addition of appendix previously added to a country-specific French protocol amendment to the global amendment. (Consolidation of PA6 & PA 6.1 [France] protocols)
Throughout, as needed	Minor changes.	Clarification/correction.

18.6. 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 it 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 protocol deviations related to the pandemic.

   b) Study monitors may be unable to carry out source data review or source data verification, 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 study 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:

   a) There may be an increased amount of missing data because of a 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.

   b) 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.

amd-8-prot-KTE-C19-105

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	29-Jan-2024 17:02:20