CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19)
Protocol Number:	KT-US-471-0119 (ZUMA-19)
IND Number:	016278 – Axicabtagene Ciloleucel 122950 – Lenzilumab
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Version:	**Amendment 2 03 August 2021** **Amendment 1 16 September 2019**
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CONFIDENTIALITY NOTICE

Sponsor and Investigator Signature Page

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STUDY ACKNOWLEDGMENT

A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19)

Amendment 2.0, 03 August 2021

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

PPD

PPD

Kite Medical Monitor Name (Printed)

September 1, 2021 | 9:52:17 AM PDT

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 one 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

Site Number

PROTOCOL SYNOPSIS

Title	A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19)
Indication	Relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Study Design	This is a Phase 1/2, open-label, multicenter study evaluating lenzilumab use to prevent axicabtagene ciloleucel treatment-related toxicities in subjects with relapsed or refractory large B-cell lymphoma. The addition of lenzilumab to the approved axicabtagene ciloleucel treatment regimen will hereafter be referred to as sequenced therapy. In Phase 1, a 3+3 design will be used to determine the recommended Phase 2 dose (RP2D) of lenzilumab within sequenced therapy for large B-cell lymphoma. The RP2D of lenzilumab will be determined primarily by clinical assessment of the incidence of dose-limiting toxicity (DLT) related to sequenced therapy. In addition to evaluation of DLT incidence, the extent of granulocyte macrophage-colony stimulating factor (GM-CSF) axis suppression as assessed by translational analysis may be assessed in defining the RP2D. Once the RP2D is determined, the study will convert to Phase 2 and assume a Simon 2-stage design. After 14 subjects have been treated with sequenced therapy at the RP2D of lenzilumab and followed for 28 days across Phase 1 and Phase 2, futility of sequenced therapy to demonstrate a significant decrease, compared to historical controls, in the incidence of Grade 2 or higher neurologic events will be assessed. If the futility threshold is not met, an additional 16 subjects will be treated with sequenced therapy at the RP2D of lenzilumab to complete accrual. In total, approximately 36 subjects will be enrolled and treated during the study. In Phase 1, a Safety Review Team (SRT) will pause enrollment to review safety data after 3 and 6 (as needed) subjects have been followed for 28 days after sequenced therapy in each dose escalation cohort. At the conclusion of dose escalation, the SRT will determine the RP2D of lenzilumab and conversion to Phase 2. The SRT can meet more often if needed.

	Once the study converts to Phase 2, the SRT will convene after a total of 14 subjects have been treated at the RP2D across Phase 1 and Phase 2, and have been followed for at least 28 days after axicabtagene ciloleucel administration. At this time, enrollment will be paused for safety data review and interim/futility analysis. If the SRT determines that the study does not meet criteria for futility, an additional 16 subjects will be enrolled to complete accrual.
Study Objectives	In Phase 1, the primary objective of the study is to evaluate the safety of sequenced therapy with lenzilumab and axicabtagene ciloleucel in subjects with refractory large B-cell lymphoma. In Phase 2, the primary objective is to evaluate the incidence of Grade 2 or higher neurologic events with sequenced therapy given at the RP2D of lenzilumab in subjects with relapsed or refractory large B-cell lymphoma. The secondary objectives are to evaluate the safety and efficacy of sequenced therapy, the extent of GM-CSF axis suppression in the blood, and the levels of chimeric antigen receptor (CAR) T cells and cytokines in the blood
Study Hypothesis	No formal hypothesis will be tested in Phase 1 of this study. In the Phase 2, this study is designed to differentiate between a treatment that has a Grade 2 or higher neurologic event rate of 45%, as seen in ZUMA-1 Cohorts 1 and 2, and a treatment with a Grade 2 or higher neurologic event rate of 20% or less. The hypothesis is that the Grade 2 or higher neurologic event rate for subjects treated with sequenced therapy at the RP2D of lenzilumab is significantly less than 45%.
Primary Endpoints	• Phase 1: Incidence of DLTs related to sequenced therapy with lenzilumab and axicabtagene ciloleucel • Phase 2: Incidence of Grade 2 or higher neurologic events within 28 days of axicabtagene ciloleucel administration
Secondary Endpoints	• Safety of sequenced therapy, as measured by the incidence of adverse events (AE) and serious AEs, including cytokine release syndrome and neurologic events • Efficacy of sequenced therapy, as measured by analysis of objective response rate (complete response [CR] + partial response), CR rate, duration of response, overall survival, and progression-free survival • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines (including free GM-CSF) in blood

CCI [redacted]	[redacted]
Sample Size	Approximately 36 subjects: • Phase 1: approximately 3 to 12 subjects • Phase 2: approximately 8 to 24 subjects
Study Eligibility	Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study.
Treatment	Lymphodepleting chemotherapy: • Lymphodepleting chemotherapy consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day will be administered for 3 days, prior to axicabtagene ciloleucel infusion. Investigational product treatments: • Lenzilumab treatment consists of an intravenous (IV) infusion on Day 0, 6 hours prior to axicabtagene ciloleucel, in the following dose cohorts: Cohort 1: 600 mg IV administered on Day 0 Cohort 2: 1800 mg IV administered on Day 0 • Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered IV on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. CCI [redacted]

Procedures	At specific time points as outlined in the schedule of assessments (SOA), subjects will undergo the following assessments/procedures: collection of informed consent, general medical history including previous treatments for non-Hodgkin's lymphoma, physical examinations (including vital signs and performance status), neurologic assessments, blood draws for complete blood count, chemistry panels, cytokine levels, C-reactive protein, lymphocyte subsets, anti-axicabtagene ciloleucel antibodies, replication-competent retrovirus, 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, echocardiogram, brain magnetic resonance image, a positron emission tomography–computed tomography, and possible bone marrow aspirate or biopsy prior to enrollment and associated leukapheresis. Subjects will have lumbar punctures performed for the collection of CSF (see Section 7.9 and SOA) before and after axicabtagene ciloleucel infusion. Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and AEs and will have their disease assessed.
Safety Review Team	The SRT will be specifically chartered to review safety data during the dose escalation portion of the study and make recommendations on further study conduct based on the incidence of DLTs, AEs, and translational assessment of GM-CSF axis suppression. In Phase 1, the SRT will meet after the first 3 and 6 subjects are treated in each dose escalation cohort with axicabtagene ciloleucel and lenzilumab and have had the opportunity to be followed for 28 days after the last axicabtagene ciloleucel dose. The SRT can meet more often if needed. In Phase 2, the SRT will meet to assess safety data and futility of sequenced therapy with lenzilumab and axicabtagene ciloleucel to significantly reduce the incidence of Grade 2 or higher neurologic events after axicabtagene ciloleucel treatment once 14 subjects have been treated at the RP2D and have been followed for 28 days after the last axicabtagene ciloleucel dose, through an interim analysis.
Statistical Considerations	The primary endpoint for Phase 1 is the incidence of DLTs related to sequenced therapy with lenzilumab and axicabtagene ciloleucel. The primary endpoint for Phase 2 is the incidence of Grade 2 or higher neurologic events 28 days after administration of axicabtagene ciloleucel. This endpoint will be based on a primary objective analysis set consisting of all subjects enrolled in the RP2D cohort and treated with axicabtagene ciloleucel at a minimum dose of CCI anti-CD19 CAR T cells/kg CCI

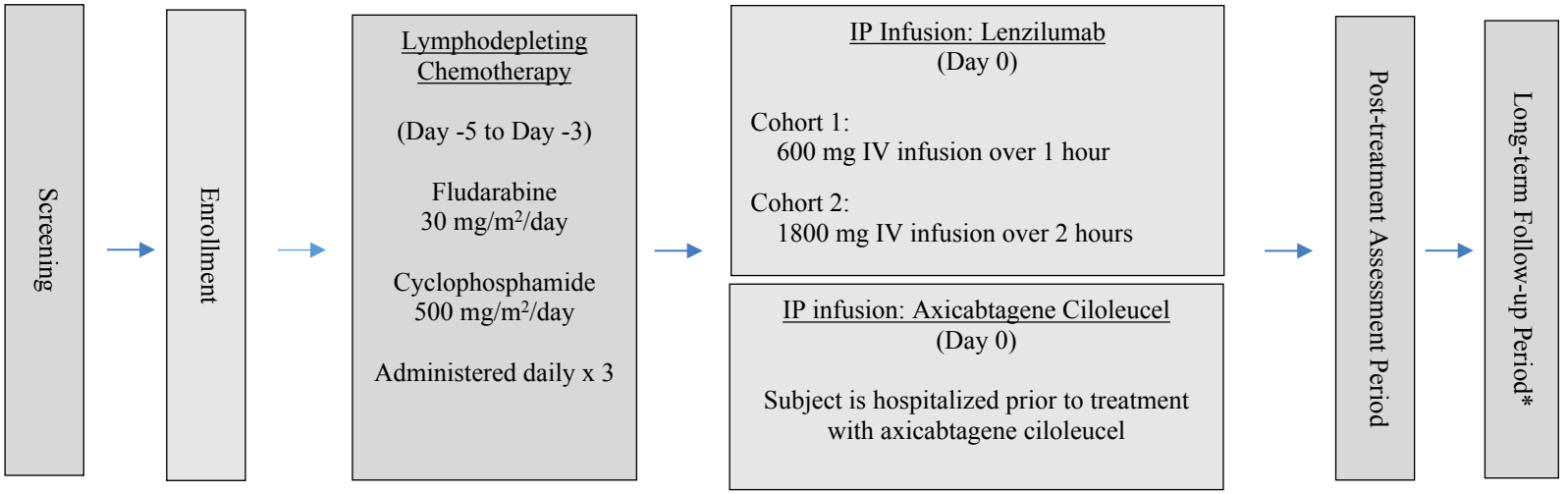
	CCI [redacted] and any dose of lenzilumab prior to axicabtagene ciloleucel infusion. In Phase 2, this study uses a Simon 2-stage design to evaluate the incidence of Grade 2 or higher neurologic events in this study compared with the incidence observed in the pivotal study of axicabtagene ciloleucel (ZUMA-1 Cohorts 1 and 2). This study has an 80% power to distinguish a therapy with a ≤ 20% rate of Grade 2 or higher neurologic events from a therapy with a ≥45% rate of Grade 2 or higher neurologic events (the rate seen in ZUMA-1 Cohorts 1 and 2) with a 1-sided alpha level of 0.025. At primary analysis, the null hypothesis will be rejected if ≤ 8 subjects experience Grade 2 or higher neurologic events are observed in 30 subjects. Prior to primary analysis, a futility analysis will be conducted at the conclusion of Stage 1 of Phase 2, when 14 subjects have been treated at the RP2D and followed for 28 days after axicabtagene ciloleucel treatment. If ≥ 5 of the initial 14 subjects had Grade 2 or higher neurologic events, the study may be stopped for futility at the discretion of the SRT. This assessment has an 83.28% chance of stopping when no treatment effect is likely to be seen.

STUDY GLOSSARY

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
BBB	Blood brain barrier
CAR	Chimeric antigen receptor
CBC	Complete blood count
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CPF	Cell processing facility
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
eACT™	Engineered autologous cell therapy
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full analysis set
FL	Follicular lymphoma
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
HGBL	High-grade B-cell lymphoma
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICE	Immune effector cell-associated encephalopathy
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IFN-γ	Interferon-gamma
IP	Investigational product
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous(ly)

IWG	International Working Group
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
MCP-1	Monocyte chemoattractant protein-1
MIP-1α	Macrophage inflammatory protein-1α
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PAP	pulmonary alveolar proteinosis
PET-CT	Positron emission tomography–computed tomography
PBMC	Peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PMBCL	Primary mediastinal large B-cell lymphoma
PR	Partial response
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RCR	Replication-competent retrovirus
RP2D	Recommended Phase 2 dose
r/r	relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SOA	Schedule of assessments
SRT	Safety Review Team
TFL	Transformed follicular lymphoma
WBC	White blood cell

Figure 1. Study Schema (Phase 1 and Phase 2)



- Collection of peripheral blood mononuclear cells from the subjects will occur through leukapheresis performed at study enrollment.
- Lymphodepleting chemotherapy consists of administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 for 3 consecutive days (Day -5 through Day -3).
- Investigational Products: Lenzilumab will be administered on Day 0 at a dose determined by dose cohort as above 6 hours prior to axicabtagene ciloleucel infusion. Axicabtagene ciloleucel consists of a single IV infusion of a target of 2 × 10^6 anti-CD19 transduced autologous CAR T cells/kg CCI [redacted] CCI [redacted] administered on Day 0.
  *After the end of KT-US-471-0119, subjects who received an infusion of axicabtagene ciloleucel will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968.

Abbreviations: CAR, chimeric antigen receptor; IP, Investigational Product; IV, intravenous.

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1. OBJECTIVES

1.1. Primary Objective

- The primary objective of Phase 1 of the study is to evaluate the safety of sequenced therapy with lenzilumab and axicabtagene ciloleucel in subjects with relapsed or refractory large B-cell lymphoma.

- In Phase 2, the primary objective is to evaluate the incidence of Grade 2 or higher neurologic events with sequenced therapy given at the recommended Phase 2 dose (RP2D) of lenzilumab in subjects with relapsed or refractory large B-cell lymphoma.

1.2. Secondary Objectives

- Secondary objectives will include evaluating the safety and efficacy of sequenced therapy, the extent of granulocyte macrophage-colony stimulating factor (GM-CSF) axis suppression in the blood, and the levels of chimeric antigen receptor (CAR) T cells and cytokines in the blood.

2. DISEASE BACKGROUND AND RATIONALE

2.1. Disease Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes and, to a lesser extent, in T lymphocytes or natural killer cells. For 2019, the United States Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program estimated that there will be 74,200 new cases of NHL and over 19,970 deaths related to the disease. NHL is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women, accounting for 4% of all new cancer cases and approximately 3% of deaths related to cancer {Howlader 2017}.

Diffuse large B-cell lymphoma (DLBCL) is an aggressive NHL subtype that accounts for approximately 30% of NHL cases worldwide {Al-Hamadani 2015, Perry 2016, Rodriguez-Abreu 2007, Teras 2016}. Incidence varies by region, with age-adjusted incidence of 5.6 cases per 100,000 persons reported by the SEER program and 3.13 per 100,000 persons reported from cancer registries in the EU {National Cancer Institute (NIH) 2019, Sant 2010}. The addition of rituximab into combination therapies for DLBCL, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), has greatly improved patient outcomes. However, it is estimated that 30% to 40% of patients are refractory to R-CHOP, and these patients have a particularly dire prognosis {Coiffier 2016, Flowers 2010}.

Other aggressive NHL subtypes include primary mediastinal large B-cell lymphoma (PMBCL), transformed follicular lymphoma (TFL), and high-grade B-cell lymphoma (HGBL). PMBCL accounts for < 3% of all B-cell lymphomas and is thought to arise from thymic (medullary) B cells, with histology similar to DLBCL and a gene-expression pattern similar to classical Hodgkin lymphoma {National Comprehensive Cancer Network 2019, The Non-Hodgkin's Lymphoma Classification Project 1997}. TFL arises from follicular lymphoma (FL), the most common indolent form of NHL (approximately 20% to 30%), with histological transformation to DLBCL at an annual rate of approximately 3% for 15 years and decreasing in subsequent years. HGBL is a very aggressive lymphoma phenotypically intermediate between DLBCL and Burkitt's lymphoma. HGBL includes lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements (previously termed double- or triple-hit lymphomas) that have poor outcome compared with DLBCL. While R-CHOP is a first-line therapy option for PMBCL and TFL, it is generally an ineffective therapy for HGBL. Patients with relapsed/refractory (r/r) HGBL, PMBCL, and TFL have a similar or worse prognosis relative to those with refractory DLBCL, although no large prospective studies have been conducted in r/r PMBCL or r/r TFL {Kuruvilla 2008, National Comprehensive Cancer Network 2019}.

SCHOLAR-1, a large multicenter, patient-level retrospective study, examined outcomes of refractory DLBCL, PMBCL, and TFL using pooled data from 2 randomized Phase 3 clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). For the study, refractory DLBCL was defined as progressive disease (PD) or stable disease (SD) as the best response at

any point during chemotherapy (≥ 4 cycles of first-line or 2 cycles of later-line therapy) or relapsed ≤ 12 months of autologous stem cell transplantation. The study highlighted the poor prognosis of patients affected with refractory DLBCL, reporting that the pooled patient population with refractory disease (N = 636) had an objective response rate (ORR) to the next line of therapy of 26% (complete response [CR], 7%), and a median overall survival (OS) of only 6.3 months {Crump 2017}.

These discouraging results demonstrate that new treatment options are needed for patients whose tumors do not respond to chemotherapy. The recently approved anti-CD19 CAR T-cell products are a promising treatment option for patients with relapsed or refractory large B-cell lymphoma.

2.2. Axicabtagene Ciloleucel

2.2.1. Product Description

Axicabtagene ciloleucel is a CD19-directed, genetically modified, autologous T-cell immunotherapy. For this therapy, a patient's T cells are genetically modified to produce a chimeric antigen receptor (CAR) protein, allowing the T cells to identify and eliminate CD19-expressing normal and malignant cells. CD19 is expressed by most B-cell malignancies {Leonard 2001, Olejniczak 2006, Rodriguez 1994, Uckun 1988}, as well as normal B lymphocytes in peripheral blood and the spleen, but not by granulocytes, monocytes, platelets, erythrocytes, and T lymphocytes {Uckun 1988}. Briefly, the anti-CD19 CAR transgene comprises the following key domains: 1) an extracellular antihuman CD19 single-chain variable region fragment derived from the monoclonal antibody FMC63; 2) the transmembrane costimulatory domain CD28; and 3) the cytoplasmic portion of human CD3ζ that includes the signaling domains {Nicholson 1997}. Following CAR engagement with $CD19^+$ target cells, the costimulatory domains activate a downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector function.

2.2.2. Axicabtagene Ciloleucel Approval

On 18 October 2017, the Food and Drug Administration (FDA) approved axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, HGBL, and TFL {YESCARTA 2019}.

FDA approval was based on ZUMA-1 (Cohorts 1 and 2), a single-arm, multicenter study of 108 adult subjects with relapsed or refractory aggressive large B-cell NHL {Neelapu 2017}. In the 101 subjects treated in Phase 2, the ORR was 83%, and the CR rate was 58%. At a median follow-up of 27.1 months, 37% of subjects remained in remission, highlighting the durability of responses achieved with axicabtagene ciloleucel over time. Median OS was not reached and 50.5% of subjects remained alive at 24 months {Locke 2019}. The most common Grade 3 or higher adverse events (AEs) in all 108 subjects (incidence of ≥ 10%) were febrile neutropenia, fever, cytokine release syndrome (CRS), encephalopathy, infections (pathogen unspecified), hypotension, hypoxia, and lung infections. Serious adverse reactions occurred in 52% of subjects and included, but were not limited to, encephalopathy, fever, febrile neutropenia, and serious infections. Grade 3 or higher CRS and neurologic events were reported for 13% and 31% of

subjects, respectively {YESCARTA 2019}, and 1 fatal case of CRS occurred {Locke 2019}. FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy to mitigate the risk of CRS and neurologic events {YESCARTA 2019}.

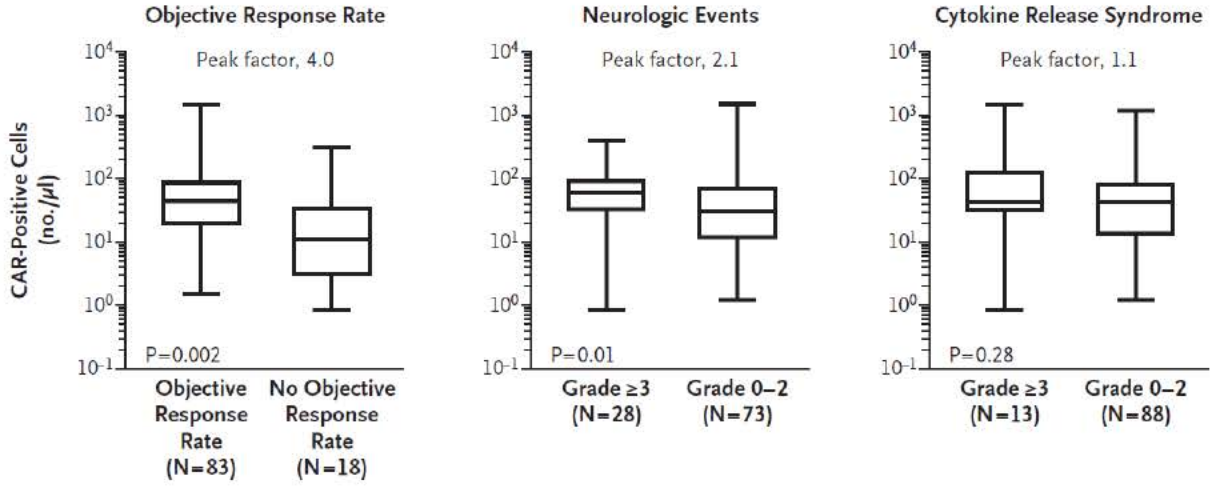
The dose of axicabtagene ciloleucel is a single intravenous (IV) infusion with a target of 2 x 10^6 CAR -positive viable T cells per kg body weight (maximum 2 x 10^8), preceded by cyclophosphamide and fludarabine lymphodepleting chemotherapy {YESCARTA 2019}. Additional details regarding the mechanism of action and clinical results of axicabtagene ciloleucel can be found in the Investigator's Brochure (IB).

2.2.3. Strategies to Mitigate Risks Associated With Axicabtagene Ciloleucel

Despite the success of axicabtagene ciloleucel, patients may require intensive care to mitigate morbidity and mortality caused by CRS and neurologic events. In many cases, CRS can be ameliorated by administration of the interleukin-6 (IL-6) receptor antagonist antibody tocilizumab, but case studies and retrospective analysis suggest neurologic events may be unaffected by tocilizumab treatment {Gust 2017, Lee 2014, Santomasso 2018}. Furthermore, ZUMA-1 cohort 3 demonstrated that prophylactic tocilizumab alone possibly worsens the incidence of neurologic events {Locke 2017a}.

There are no approved therapies available for the prevention or the treatment of neurologic events associated with CAR T-cell therapy. Identification of mitigation strategies is complicated by a statistically significant association between CAR T-cell expansion and both the likelihood of objective response and with the likelihood of observing a Grade 3 or higher neurologic event in the ZUMA-1 study. This finding suggests a direct correlation between efficacy and toxicity with anti-CD19 CAR T-cell therapy (Figure 2) {Neelapu 2017}. Systemic corticosteroids are currently used to treat neurologic events through broad suppression of the immune system. Whether corticosteroid treatment therefore blunts the clinical activity of CAR T-cells is as yet unresolved; clinical trials assessing this important question are underway. However, alternative strategies to improve the safety profile of CAR T-cell therapy without negatively impacting efficacy should be investigated.

Figure 2. Correlation Between CAR T-cell Expansion, Efficacy, and Safety



CAR, chimeric antigen receptor.

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

The design and rationale of this study is in part derived from prior experience with axicabtagene ciloleucel on other Kite Pharma, Inc.-sponsored studies, including ZUMA-1. Refer to the current axicabtagene ciloleucel IB for the most current anti-CD19 CAR T-cell nonclinical and clinical information.

2.4. Rationale for GM-CSF Neutralization With CAR T-cell Therapy

2.4.1. GM-CSF Level Correlation With CAR T-cell Therapy-related Toxicities

Much has been learned regarding the possible mechanisms and pathophysiology of neurologic events related to CAR T-cell therapy, including the role of myeloid cells and proinflammatory cytokines. In ZUMA-1, several cytokines were significantly associated with Grade 3 or higher neurologic events, including GM-CSF, a soluble immune-modulating cytokine {Locke 2017b, Neelapu 2017}. However, there was no direct association between GM-CSF levels and overall response {Rossi 2016}, suggesting that GM-CSF inhibition may have the potential to decouple toxicity from efficacy of anti-CD19 CAR T cells. Increased GM-CSF levels have also been associated with CRS. In a study of 51 subjects with r/r acute lymphoblastic leukemia, Grade 4 or higher CRS was associated with increased levels of several cytokines and chemokines including interferon-gamma (IFN-γ), IL-6, IL-8, CCL2 (monocyte chemoattractant protein 1 [MCP-1]), CCL3 (macrophage inflammatory protein-1α [MIP-1α]), and GM-CSF {Teachey 2016}.

Generally considered a myeloid inflammatory factor, GM-CSF serves as a communication conduit between activated lymphocytes that express GM-CSF and nonspecific inflammatory myeloid cells that express the GM-CSF receptor. Outside the context of inflammation, animals lacking either GM-CSF or its receptor display no severe perturbation in myelopoiesis or the myeloid system generally, with the exception of alveolar macrophage dysfunction {Becher 2016}. Preclinical models demonstrate that GM-CSF signaling drives numerous functions of

mature tissue macrophages, such as cell adhesion, expression of pathogen recognition receptors, and proinflammatory cytokines (tumor necrosis factor-α, IL-12, IL-18, IL-6, MCP-1, and macrophage colony stimulating factor-1), phagocytosis, and microbial killing {Shibata 2001}. Recent preclinical models of CAR T-cell therapy-related CRS and neurologic events indicate that CAR T cells produce GM-CSF upon tumor challenge in vitro and in vivo, and monocytes are the primary source of toxicity-related proinflammatory cytokines, such as IL-1, IL-6, and IL-8 {Barrett 2016, Giavridis 2018, Norelli 2018, Sterner 2019}.

GM-CSF levels are elevated within 1 day after CAR T-cell infusion and peak in 2 to 3 days {Roberts 2018, Rossi 2016}, suggesting its role as an initiator of an inflammatory cascade. Other cytokines have been associated with Grade 3 or higher neurologic events, including IL-15, IL-6, IL-1Ra, IL-2α, IFN-γ, IL-10, IL-8, MCP-1 {Locke 2017b}; however, many of these cytokines peak later after CAR T-cell infusion or are directly related to T-cell expansion {Roberts 2018}. Once activated by T cell-derived GM-CSF, myeloid cells are capable of expansion, trafficking, and cytokine production that fosters further myeloid cell recruitment, which exacerbates the inflammatory cascade {Spath 2017}. It is possible that once initiated, this inflammatory cascade can become a self-perpetuating "storm," resulting in further activation, expansion, and trafficking of myeloid cells, abnormally high levels of inflammatory cytokines, endothelial cell activation, vascular permeability, and ultimately neurologic events. As such, inhibition of a key early driver of the inflammatory cascade may be more effective in reducing both the frequency and severity of neurologic events.

2.4.2. GM-CSF Neutralization in Preclinical Models of CAR T-cell Toxicity

Preclinically, GM-CSF neutralization with the anti-GM-CSF antibody lenzilumab, has demonstrated that toxicities related to anti-CD19 CAR T-cell therapy can be effectively prevented in vivo {Sterner 2019}. Blood-brain-barrier (BBB) disruption, allowing the infiltration of immune cells and proinflammatory cytokines into the central nervous system (CNS), has been shown to be an important factor in the pathogenesis of neurologic events related to CAR T-cell therapy. Both preclinical in vivo studies and clinical trials have demonstrated BBB impairment following CAR T-cell therapy, enabling both immune cell neuroinfiltration and marked elevation of inflammatory cytokines in the CNS {Santomasso 2018, Sterner 2019, Taraseviciute 2018}. In the preclinical model of sequenced lenzilumab and CAR T-cell therapy, quantification of magnetic resonance imaging (MRI) gadolinium-enhanced T1 hyperintensities showed a 75% decrease in neuroinflammation and BBB impairment when lenzilumab was added to anti-CD19 CAR T-cell therapy versus anti-CD19 CAR T-cell therapy alone. When lenzilumab was added to anti-CD19 CAR T-cell therapy, body weight and cytokine levels were more similar to that seen in mice infused with untransduced T cells, suggesting CRS was prevented. Despite the improvement in toxicities related to anti-CD19 CAR T-cell therapy, disease control was not impaired by the addition of lenzilumab to anti-CD19 CAR T-cell therapy in vivo. Furthermore, GM-CSF neutralization with lenzilumab may even enhance efficacy of anti-CD19 CAR T therapy by reducing the rate of relapse and improving the durability of response, as demonstrated in this model {Sterner 2019}. Taken together, these preclinical findings suggest that the addition of lenzilumab to anti-CD19 CAR T-cell therapy has the potential to improve safety, without harming anti-CD19 CAR T-cell therapy efficacy, breaking the link between efficacy and toxicity observed with anti-CD19 CAR T-cell therapy.

2.5. Lenzilumab

2.5.1. Product Description

Lenzilumab is a first-in-class Humaneered® recombinant monoclonal antibody targeting soluble human GM-CSF, with potential immunomodulating activity, high binding affinity in the pM range, and 94% specificity to the human germline, which reduces immunogenicity. Upon administration, lenzilumab binds to and neutralizes GM-CSF. This prevents GM-CSF binding to the GM-CSF receptor, which is a heterodimeric protein expressed on myeloid progenitor cells, and prevents GM-CSF-mediated signaling.

2.5.2. Summary of Clinical Studies for Lenzilumab

Clinical experience to date with lenzilumab is summarized in Table 1. As of July 2019, lenzilumab has been administered to a total of 114 subjects at various dose levels in 4 studies.

Table 1. Clinical Experience With Lenzilumab

Protocol	Title	Subjects	Status
HGEN003-01	Single-dose Lenzilumab in Healthy Adult Volunteers	12	Completed
HGEN003-02	Study of Lenzilumab in Biologics-Inadequate Rheumatoid Arthritis	9	Terminated
HGEN003-04	Effect of Lenzilumab in Subjects with Asthma Inadequately Controlled by Corticosteroids	160	Completed
HGEN003-05	Study of Lenzilumab in Subjects with Relapsed or Refractory Chronic Myelomonocytic Leukemia (CMML)	15	Ongoing

Study HGEN003-01 was a Phase 1 dose escalation study assessing 1, 3, or 10 mg/kg of lenzilumab in healthy subjects. Nine subjects received lenzilumab (3 subjects per dose), and 3 subjects received placebo. The regimen was well tolerated with no observed dose-limiting toxicities (DLTs). All 7 observed treatment-emergent AEs (TEAEs) were Grade 1 in severity, with 1 TEAE considered possibly related to study treatment (hot flush that resolved within 1 hour without treatment). Study HGEN003-02 assessed lenzilumab in subjects with rheumatoid arthritis and was terminated after the safety run-in was complete due to changes in corporate direction. The safety run-in included 7 subjects who received 600 mg lenzilumab IV and 2 subjects who received placebo on Weeks 0, 2, 4, 8, and 12. All TEAEs observed were Grade 1 or Grade 2 in severity and similar to those reported with placebo.

Study HGEN003-04 was a Phase 2 randomized, double-blind, placebo-controlled study of lenzilumab in subjects with asthma inadequately controlled with long-acting bronchodilators and inhaled/oral corticosteroids. Subjects received 400 mg lenzilumab IV (n = 78) or placebo (n = 82) at Weeks 0, 2, 4, 8, 12, 16, and 20. Forty-eight subjects (61.5%) who received lenzilumab and 41 subjects (50.0%) who received placebo had ≥ 1 TEAE. TEAEs reported to occur with an overall incidence rate > 5% were nasopharyngitis, upper respiratory tract infection, and headache; these events were all considered Grade 1 or Grade 2 in severity and occurred at a similar rate to the placebo group. Six serious AEs (SAEs) were reported for 5 of 78 subjects

(6.4%) who received lenzilumab and 4 SAEs were reported for 2 of 82 subjects (2.4%) who received placebo. For subjects who received lenzilumab, SAEs included 2 cases of pneumonia and 1 case each of acute myocardial infarction, appendicitis, suicide attempt, and hypoxia; for subjects who received placebo, SAEs included 1 case each of diarrhea, thrombosis in device, anaphylactic reaction, and bacterial arthritis. No SAEs were considered as possibly related to treatment. Sixteen Grade 1 and Grade 2 infusion-related reactions were reported (6 events in 4 subjects who received lenzilumab and 10 events in 2 subjects in the placebo group), but all were either self-limiting or resolved upon treatment with no sequelae {Molfino 2016}.

HGEN003-05 is a multicenter Phase 1 study designed to evaluate the safety and determine the RP2D of lenzilumab in subjects with chronic myelomonocytic leukemia (CMML). Dose escalation proceeded using a standard 3+3 study design to determine the maximum tolerated dose. Three dose cohorts included 200, 400, and 600 mg, given IV on Day 1 and 15 of cycle 1 and then only on Day 1 of subsequent 28-day cycles. Three subjects were enrolled at each dose level and an additional 6 subjects were enrolled at 600 mg as planned. No DLTs were identified, and no treatment-emergent Grade 3 or 4 toxicities were reported. Pharmacokinetic analysis and pharmacodynamics were also evaluated. The mean duration on therapy was 221.8 days (range: 14 to 787 days). Durable clinical benefit was achieved in 33% of subjects and 1 subject was bridged to allogenic transplant, providing proof of concept that GM-CSF neutralization has activity in CMML. The median age at study entry was 74 years (range: 62 to 85 years), and 80% were male. Nine subjects were classified as CMML-0, 3 as CMML-1, and 3 as CMML-2. Nine subjects were previously treated with hypomethylating agents and/or experimental therapies, 4 were treated with hydroxyurea, and 3 were untreated. The mean hemoglobin was 9.7g/dL (range: 7.6 to 14g/dL), the mean platelet count was 147 x 10^3 cells/dL (range: 16 to 942 x10^3 cells/dL), and 66% of cases were myeloproliferative neoplasms-CMML by the French-American-British classification at study entry. The safety profile of lenzilumab was consistent with that reported in prior studies.

One theoretical concern regarding GM-CSF neutralization as a therapeutic strategy was the potential for pulmonary alveolar proteinosis (PAP) development. Autoimmune PAP can be caused by a disruption of GM-CSF signaling in alveolar macrophages, leading to surfactant accumulation in the bronchioles and gas exchange impairment {Trapnell 2019}. Patients with autoimmune PAP typically have high levels of polyclonal GM-CSF neutralizing auto-antibodies compared with healthy individuals {Inoue 2008, Kitamura 1999, Uchida 2009}. Across the 3 studies of lenzilumab, no evidence of PAP was detected as assessed by surfactant protein D levels, lactate dehydrogenase levels, oxygen saturation, chest X-rays, and pulmonary function. The risk of PAP is theorized to be reduced for a monoclonal antibody versus polyclonal antibodies directed towards GM-CSF, since the monoclonal antibody off-rate could allow for a basal level of GM-CSF signaling by alveolar macrophages.

As a single agent, lenzilumab is well tolerated, with only mild to moderate AEs reported in 114 subjects treated in Phase 1 and 2 clinical trials. No identified risks or important potential risks were associated with lenzilumab in clinical studies. Overall, the specificity of GM-CSF neutralization toward suppression of a myeloid-driven inflammatory cascade, combined with the favorable safety profile of lenzilumab provides a rationale for adding lenzilumab to the axicabtagene ciloleucel treatment regimen. Rationale specific to the dosing of lenzilumab is described in Section 6.2.3.

3. STUDY DESIGN

3.1. General Study Design

ZUMA-19 is a Phase 1/2, open-label, multicenter study evaluating lenzilumab use to prevent axicabtagene ciloleucel treatment-related toxicity in subjects with relapsed or refractory large B-cell lymphoma. The addition of lenzilumab to the approved axicabtagene ciloleucel treatment regimen will hereafter be referred to as sequenced therapy.

ZUMA-19 will be separated into 2 distinct phases designated as the Phase 1 study and Phase 2 study.

In Phase 1, a 3+3 design will be used to determine the RP2D of lenzilumab within sequenced therapy for large B-cell lymphoma. There will be 2 dose escalation cohorts. The RP2D of lenzilumab will be determined primarily by clinical assessment of the incidence of DLTs related to sequenced therapy. In addition to evaluation of DLT incidence, the extent of GM-CSF axis suppression as assessed by translational analysis may be assessed in defining the RP2D.

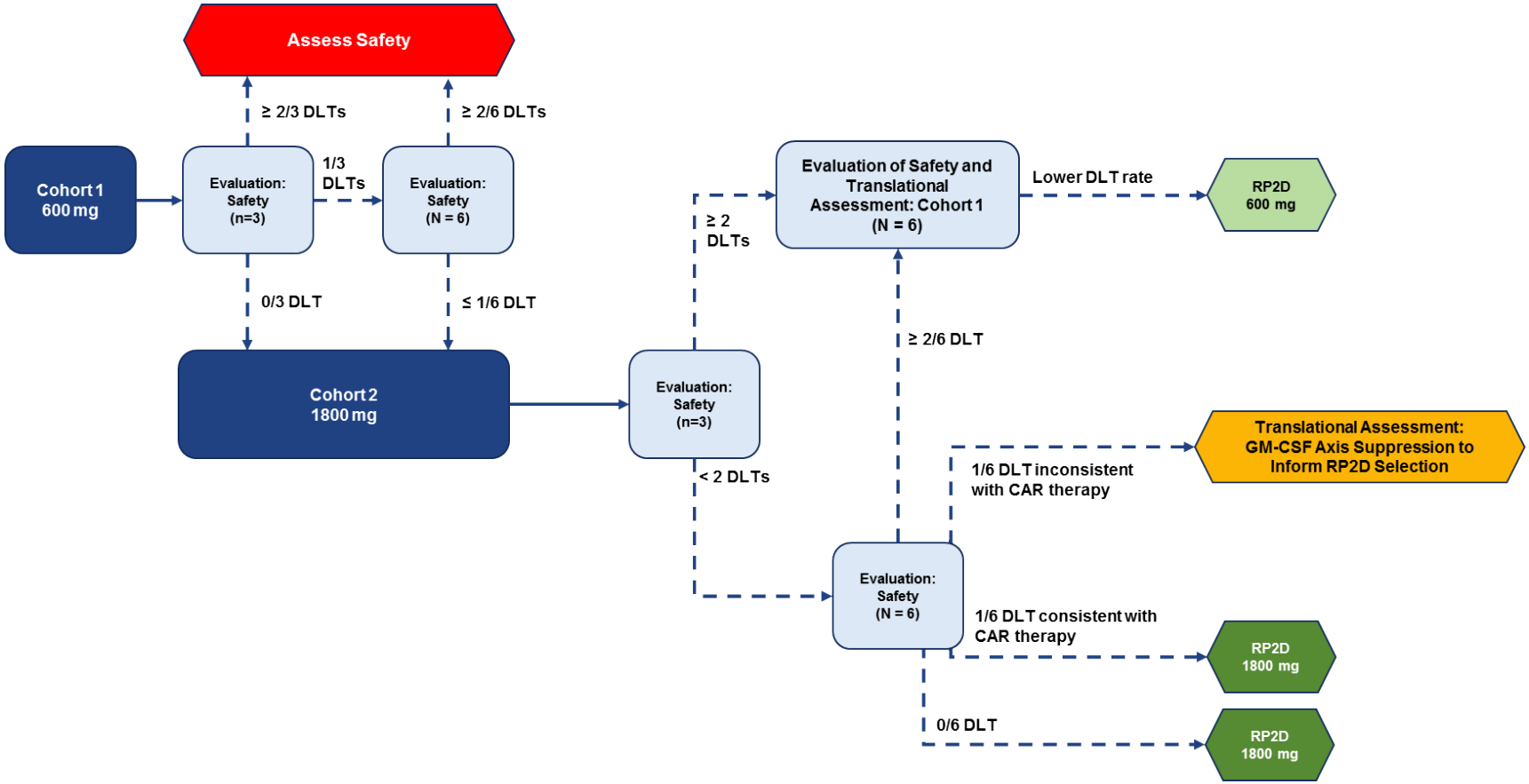
During Phase 1, a Safety Review Team (SRT) will pause enrollment to review safety data after 3 and 6 (as needed) subjects have been followed for 28 days after axicabtagene ciloleucel administration in each dose escalation cohort. At the conclusion of dose escalation, the SRT will determine the RP2D and study conversion to Phase 2. The SRT can meet more often if needed.

In Phase 2, the study will assume a Simon 2-stage design. After 14 subjects have been treated with sequenced therapy at the RP2D of lenzilumab and followed for 28 days across Phase 1 and Phase 2, futility of sequenced therapy to demonstrate a significant decrease, compared to historical controls, in the incidence of Grade 2 or higher neurologic events will be assessed. If the futility threshold is not met, an additional 16 subjects will be treated with sequenced therapy at the RP2D of lenzilumab to complete accrual.

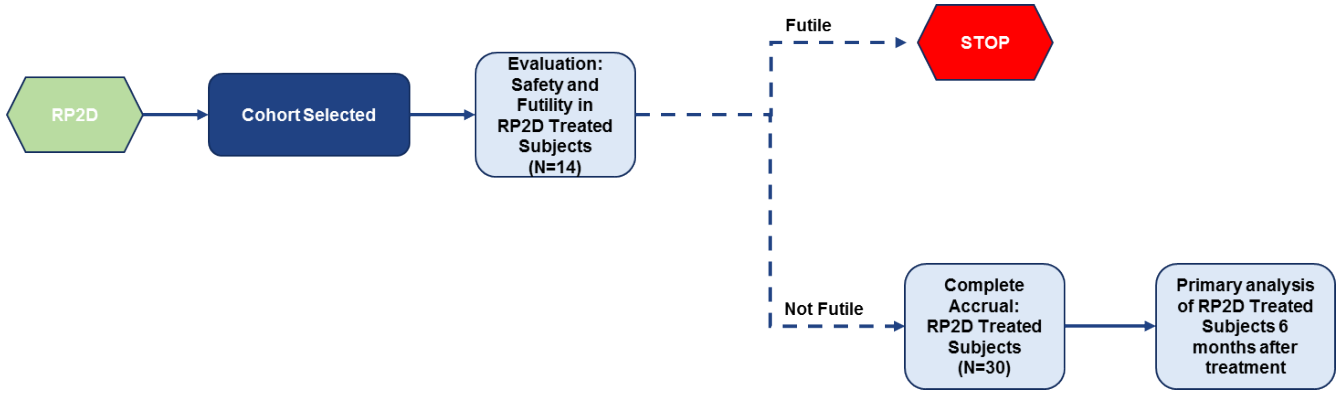
In total, this Phase 1/2 study will enroll approximately 36 subjects to evaluate the incidence of Grade 2 or higher neurologic events related to sequenced therapy.

Figure 3. Schematic of Study Design

A) Phase 1



B) Phase 2



Abbreviations: CAR, chimeric antigen receptor; DLT, dose-limiting toxicity; RP2D, recommended Phase 2 dose.

3.2. Participating Sites

Approximately 12 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.

3.3. Number of Subjects

Participants in this study will be referred to as "subjects." The study intends to enroll approximately 36 evaluable subjects in total over Phase 1 and Phase 2.

It should be noted that Kite may choose to close enrollment at any time. Please refer to the statistical considerations section of the protocol for sample size estimations.

3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of evaluable subjects are attained in Phase 1 and Phase 2. Subjects who have not received the target dose of lenzilumab and axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (Section 10.6).

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary depending on a subject's screening requirements, response to treatment, survival, and if applicable, timing of transitions to the separate Long-term Follow-up (LTFU) study, KT-US-982-5968 (discussed in section 3.5.3).

The need for prolonged follow-up is based on concerns about late safety events. Subjects will be followed for potential persistence of CAR T cells, secondary expansion events, and gene transfer vector elements in treated subjects manifesting as secondary malignancy and other clinically relevant outcomes.

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes 6 months of assessments. The end-of-study for each subject is defined as the last visit on this study, or when a subject is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when 30 subjects in the primary objective analysis set have completed a 6-month disease-response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

3.5.3. Long-term Follow-up

All subjects who received an infusion of lenzilumab and axicabtagene ciloleucel will be provided the opportunity to transition to a separate LTFU study, KT-US-982-5968, where they will be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to

lenzilumab and axicabtagene ciloleucel as defined in KT-US-982-5968, presence of replication-competent retrovirus (RCR), and/or insertional mutagenesis for up to 15 years from the time of lenzilumab and axicabtagene ciloleucel infusion (also refer to Section 7.13.8).

For each subject, the final visit on this study may be combined with the subject's first visit on the LTFU study. The timing of the subject's final visit/first LTFU study visit will depend upon the timing of the collection of all the subject's data that are required for the planned analysis for this study. In KT-US-982-5968, subjects will continue assessments at timepoints contiguous with the LTFU timepoints in this study.

In some circumstances, subjects may be eligible to receive a second course of treatment after enrolling in the LTFU rollover study. Retreatment eligibility criteria are described in the KT-US-982-5968 protocol.

4. SUBJECT IDENTIFICATION ASSIGNMENT

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

5. SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

1) Adult subjects with large B-cell lymphoma, including DLBCL not otherwise specified, PMBCL, HGBL, and DLBCL arising from FL

2) Subjects must have relapsed disease after 2 or more lines of systemic therapy, OR chemorefractory disease defined as the following:

   - No response to first-line therapy, including the following:

     — PD as best response to first therapy

     — SD as best response after ≥ 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP), with SD duration no longer than 6 months from the last dose of therapy

     — Note: Subjects who are intolerant to first-line chemotherapy are excluded

     OR

   - No response to ≥ 2 lines of therapy, including the following:

     — PD as best response to most recent therapy

     — SD as best response after ≥ 2 cycles of last line of therapy

3) Subjects must have received adequate prior therapy including at a minimum:

   - Anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
   - An anthracycline-containing chemotherapy regimen
   - Subjects with transformed FL must have chemorefractory disease after transformation to DLBCL

4) At least 1 measurable lesion according to the International Working Group (IWG) Lugano Classification {Cheson 2014}. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.

5) Magnetic resonance imaging of the brain showing no evidence of CNS lymphoma

6) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time the subject is planned for leukapheresis, 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 at the time the subject is planned for leukapheresis (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists).

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

8) Age 18 or older

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

10) Subjects with a known medical history of tuberculosis or a risk for tuberculosis exposure require negative tuberculosis testing by either tuberculin skin test or interferon gamma release assay.

11) Adequate bone marrow function as evidenced by:

- Absolute neutrophil count ≥ 1000/μL
- Platelets ≥ 75,000/μL
- Absolute lymphocyte count ≥ 100/μL

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

- Creatinine clearance (Cockcroft-Gault) ≥ 60 mL/min
- Serum alanine aminotransferase or aspartate aminotransferase ≤ 2.5 upper limit of normal
- Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's Syndrome
- Cardiac ejection fraction ≥ 50% with no evidence of clinically significant pericardial effusion as determined by echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings
- No clinically significant pleural effusion
- Baseline 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) History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) or FL unless disease free for at least 3 years

2) History of Richter's transformation of chronic lymphocytic leukemia

3) Autologous stem cell transplant (SCT) within 6 weeks of planned axicabtagene ciloleucel infusion

4) History of allogeneic stem cell transplantation

5) Prior CD19 targeted therapy or prior CAR T cell therapy.

6) History of PAP

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

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

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

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

11) Subjects with detectable CSF malignant cells, or brain metastases, or with a history of CNS lymphoma, CSF malignant cells or brain metastases

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

13) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

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

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

16) Primary immunodeficiency

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

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

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

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

21) 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

22) Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of lenzilumab and axicabtagene ciloleucel

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

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

6. PROTOCOL TREATMENT

6.1. Study Treatment

- The investigational products for this study are named lenzilumab and axicabtagene ciloleucel,which will be administered as sequenced therapy.
- The term study treatment refers to all protocol-required therapies.

6.1.1. Leukapheresis

Leukapheresis refers to the procedure for collecting peripheral blood mononuclear cells (PBMCs) that are used to manufacture the subject-specific axicabtagene ciloleucel. Subjects will undergo leukapheresis to obtain T cells for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the sponsor's manufacturing facility as described in the Investigational Product Manual (IPM).

6.1.3. Lymphodepleting Chemotherapy

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

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

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

6.1.3.1. Fludarabine

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

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

6.1.3.2. Cyclophosphamide

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

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

6.1.3.3. Mesna

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

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

6.1.4. Lenzilumab

Lenzilumab is one of the investigational products for this study.

Lenzilumab is an anti-GM-CSF antibody with the ability to neutralize GM-CSF. It is formulated as a sterile, clear, colorless to slightly yellow liquid for IV administration and supplied in single-use, 10-mL vials. Each vial contains 100 mg of lenzilumab at a concentration of 10 mg/mL. Lenzilumab is provided as open-label bulk supply cartons containing 6 vials per carton. Vials should not be removed from the carton prior to dose preparation and are to be stored in the refrigerator (2°C to 8°C).

Refer to the IPM protocol supplement for details and instruction on storage and administration of lenzilumab.

To date, 114 subjects have received doses of lenzilumab IV ranging from 200 mg to 600 mg. There have been no instances of accidental overdose of subjects.

If any problems related to the use of lenzilumab or any products that support the administration of lenzilumab are identified, research staff should report the problem per the instructions in the IPM protocol supplement.

6.1.5. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is one of the investigational products for this study.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow. The cryostorage bag containing axicabtagene ciloleucel arrives frozen in a liquid nitrogen dry shipper. The bag must be stored in vapor phase of liquid nitrogen and remain frozen until the subject is ready for treatment to assure that 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 infusion process.

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

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

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

6.1.6. Concomitant Therapy

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

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in Section 6.1.7.

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

For subjects who go on to receive protocol-permitted consolidative therapy (eg, SCT), only concomitant medications related to a sequenced therapy-related SAE will be recorded.

Reporting of these concomitant medications will commence at the time the preparative regimen of the therapy commences.

For subjects who receive study drug:

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

- After this 3-month follow-up period, only targeted concomitant medication will be collected for 12 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. Targeted concomitant medications include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

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

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

Specific concomitant medication collection requirements and instructions are included in the electronic case report form (eCRF) completion guidelines.

6.1.7. Excluded Medications

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

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

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

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

GM-CSF stimulating agents (ie, sargramostim) should be avoided for 2 months after lenzilumab administration, unless used to manage PAP.

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

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

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

6.1.8. Subsequent Therapy

Subsequent therapy refers to treatment administered after axicabtagene ciloleucel infusion or standard of care that is necessary to treat a subject's disease.

Subsequent therapy administered after axicabtagene ciloleucel infusion that is necessary to treat a subject's LBCL, such as non-study-specified chemotherapy, immunotherapy, targeted agents, SCT, or radiation therapy, will be recorded for all subjects until one of the following happens: the subject transitions to the KT-US-982-5968 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.

6.1.9. Toxicity Management

To date, the following risks have been identified with axicabtagene ciloleucel/KTE-C19: CRS, neurologic events, infections, and cytopenias. Refer to Section 6 of the current IB for details regarding these events and management guidance

6.2. Study Treatment Schedule

6.2.1. Leukapheresis (Within Approximately 5 Days of Eligibility Confirmation)

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) 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**.** Once a subject commences leukapheresis, the subject is considered enrolled in the study.

Mononuclear cells will be obtained by leukapheresis (12-15 liters by apheresis with a goal to target approximately 5 to 10 x 10^9 mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the CPF as described in the IPM.

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T-cell-containing PBMC fraction. 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. Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subject's lymphodepleting chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

6.2.2. Study Treatment

6.2.2.1. Chemotherapy General Instructions

Subjects will receive a nonmyeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel in vivo. Subjects will initiate lymphodepleting chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 through Day -3. The 3-day lymphodepleting chemotherapy regimen may be administered in an outpatient setting.

Subjects will be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy. In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

6.2.2.2. Lenzilumab General Instructions

Subjects will receive lenzilumab infusion at a healthcare facility on the day of axicabtagene ciloleucel infusion, Day 0. Infusion should be initiated at least 6 hours prior to axicabtagene ciloleucel administration. Lenzilumab will be infused over 1 hour at doses of 600 mg and over 2 hours at doses of 1800 mg. Rate of infusion may be modified at the investigator's discretion for subject safety.

The following medications should be administered approximately 1 hour prior to lenzilumab infusion to prevent infusion reactions. Alternatives to the recommendations below should be discussed with the medical monitor.

- Acetaminophen 500 to 1000 mg PO or equivalent
- Diphenhydramine 12.5 to 25 mg IV, or 25 mg PO or equivalent

6.2.2.3. Axicabtagene Ciloleucel General Instructions

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility, followed by daily or more frequent monitoring at a healthcare facility for at least 7 days unless otherwise required by country regulatory agencies to monitor for signs and symptoms of CRS and neurologic toxicities. Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic events in the hospital setting, if deemed appropriate by the investigator.

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

The following medications should be administered approximately 1 hour prior to axicabtagene ciloleucel infusion and at least 6 hours after the last dose of each received. Alternatives to the recommendations below should be discussed with the medical monitor.

- Acetaminophen 500 to 1000 mg PO or equivalent
- Diphenhydramine 12.5 to 25 mg IV, or 25 mg PO or equivalent

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

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

There is no requirement to initiate levetiracetam prophylaxis of seizures with administration of axicabtagene ciloleucel. Investigators may follow their own institutional standards in regard to levetiracetam use. Previous experience from Cohorts 1 and 2 of ZUMA-1 indicates that those patients who started levetiracetam seizure prophylaxis with axicabtagene ciloleucel administration and those who either never received levetiracetam or started only after the initiation of signs and symptoms of neurologic events had comparable rates of neurologic events and no improvement in incidence of seizures.

6.2.3. Rationale for Study Treatment Dosing

6.2.3.1. Rationale for Lenzilumab Dosing in Cohorts 1 and 2

Lenzilumab has been tested extensively in 114 human subjects from doses of CCI [redacted], up to 600 mg in the setting of repeated dosing. Following single-dose administration at 600 mg, serum concentrations declined below the therapeutic threshold following 3 days of administration. Steady-state pharmacokinetic (PK) data revealed a terminal half-life of 28 days and as described in Section 2.5.2, no Grade 3 or Grade 4 treatment-emergent AEs have been reported (see the IB). There was no evidence of an increase in infections or the development of PAP at these doses.

The goal of lenzilumab therapy is to neutralize the GM-CSF burst seen after infusion of anti-CD19 CAR T cells and prevent the recruitment of myeloid cells and the initiation of the inflammatory cascade that may lead to neurologic toxicities and CRS. This suggests that lenzilumab will be required to suppress GM-CSF signaling for at least 7 days after axicabtagene ciloleucel administration.

Though 600 mg is a dose known to be safe, it may not be sufficient to entirely abrogate the GM-CSF elaborated in the serum and tissues after the anti-CD19 CAR T-cell infusion. Additional unpublished analyses suggest that a higher serum concentration of lenzilumab may be required to fully neutralize GM-CSF in the tissues. Therefore, in Cohort 2 an 1800 mg dose will be utilized to fully neutralize GM-CSF in the tissues after anti-CD19 CAR T-cell infusion. Pharmacokinetic analysis performed in Phase 1 will provide first-in-human data related to lenzilumab PK at this previously untested dose. Translational assessment of GM-CSF neutralization and downstream mediators of inflammation will help determine the extent of GM-CSF axis suppression in the serum and tissues at the respective doses.

6.2.4. Study Treatment by Agent and Phase

6.2.4.1. Lymphodepleting Chemotherapy

Phase 1 and 2:

Provided the criteria for lymphodepleting chemotherapy are met, outlined in Section 7.13.5.1., the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions:

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

6.2.4.2. Lenzilumab

Phase 1:

Cohort 1: Subjects will receive a single IV dose:

- Lenzilumab 600 mg IV over approximately 60 minutes on Day 0, initiated approximately 6 hours prior to axicabtagene ciloleucel infusion

Cohort 2: Subjects will receive a single IV dose:

- Lenzilumab 1800 mg IV over approximately 120 minutes on Day 0, initiated approximately 6 hours prior to axicabtagene ciloleucel infusion.

- The infusion rate of lenzilumab may be adjusted at the discretion of the investigator for subject safety.

An additional dose cohort may be added as required to enhance safety of sequenced therapy. This decision would be made by the SRT.

Phase 2:

Based on the DLT rate and if necessary the translational assessment of GM-CSF axis suppression seen in Phase 1, an RP2D of lenzilumab will be determined by the SRT to be used in Phase 2.

6.2.4.3. Axicabtagene Ciloleucel

Phases 1 and 2:

Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered IV at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg CCI [redacted].

7. STUDY PROCEDURES

Research staff should refer to the schedule of assessments (SOA) 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. Refer to the eCRF 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 must sign the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved 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 reconsented 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 as per country and local regulations and guidelines. Where applicable, demographic data will include sex, year of birth, race, ethnicity**,** and country of enrollment to study a possible association between these variables and subject safety and treatment effectiveness.

7.3. 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 eCRFs.

In addition to the medical history, all history related to the subject's disease, treatment, and response to treatment will be collected and must date back to the original diagnosis.

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

GM-CSF suppression may increase the risk for tuberculosis re-activation. Subjects with a medical history of tuberculosis or with risk of tuberculosis exposure should be evaluated for tuberculosis by either tuberculin skin testing or interferon gamma release assay. Risk assessment and testing methodology to be determined at the investigator's discretion or based on institutional standards of care. A negative test within 3 months of anticipated lenzilumab administration is acceptable.

7.4. Physical Examination, Vital Signs, Performance Status

Physical examinations will be performed during screening and at times noted in the SOA. Changes noted in subsequent examinations when compared to the baseline examination will be reported as an AE.

During investigational product administration, vital signs including blood pressure, heart rate, oxygen saturation, and temperature will be monitored before and after the lenzilumab and axicabtagene ciloleucel infusion and then routinely per institutional guidelines. If the subject has a fever (temperature 38.3°C or greater), vital signs will be monitored more frequently as clinically indicated.

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

7.5. Neurological Assessment

Neurological assessments will be standardized by using the Immune Effector Cell-Associated Encephalopathy (ICE) score {Lee 2019}. ICE is a 10-point, 5-question evaluation that covers orientation, naming, following commands, writing, and attention. Please refer to Appendix 3 for the exact scoring criteria.

A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before administration of sequenced therapy on Day 0, and daily during the 7-day post-infusion period, and any period of ongoing Grade 2 or higher neurologic event, as well as the Week 2, Week 4, and Month 3 visits.

7.6. Cardiac Function

Each subject's cardiac function, as measured by an ECHO, will be assessed during the screening period to confirm study eligibility. Both left ventricular ejection fraction and pericardial effusion will be assessed prior to study entrance by an ECHO. An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

To establish a baseline, an ECG will also be performed during the screening period.

7.7. Magnetic Resonance Imaging

Each subject will undergo a screening brain MRI, with contrast whenever possible or without contrast in case of contraindication, to rule out CNS metastasis during the screening period of the study. A brain MRI performed ≤ 28 days before signing the consent may be used for confirmation of eligibility.

Evaluation of any new onset of Grade 2 or higher neurologic events should include a brain MRI.

7.8. Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy may be performed at screening at the discretion of the investigator. For subjects with a potential CR to axicabtagene ciloleucel, a follow-up bone marrow aspirate and biopsy may be performed in 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. A bone marrow aspirate and biopsy is not required to confirm a CR. CCI [redacted]. Refer to Appendix 1 for treatment response assessment requirements per the IWG Lugano Classification. Bone marrow aspirate and biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated in the IB. A portion of the bone marrow sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual.

7.9. Lumbar Puncture

Subjects with symptoms of CNS malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical examination will have a lumbar puncture (LP) performed at the screening visit for examination of CSF. In addition, the LP will be performed at Day 5 after axicabtagene ciloleucel infusion as per the SOA or for subjects with new onset of Grade 2 or higher neurologic events after sequenced therapy. Opening pressures should be measured and recorded in the subject's site chart with each LP whenever possible CCI [redacted]

Adequate platelet support should be provided prior to performing an LP (eg, platelet > 50,000/mm^3). The medical monitor should be contacted in the event a Day 5 LP is not attainable related to subject status.

7.10. Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the IWG Lugano Classification {Cheson 2014} (Appendix 1). Flow cytometric and 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 undergo additional PET-CT tumor assessments after their axicabtagene ciloleucel infusion. The first of these post-treatment PET-CT tumor assessments will occur 4 weeks after infusion; subsequent assessments will occur at regular intervals throughout the post-treatment and long-term follow-up portions of the study, as highlighted in the SOA.

After 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 as per the SOA.

7.11. Laboratory

The following samples will be collected at the time points indicated in the SOA. Additional samples (eg, blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Local laboratory analysis:

- Sodium, potassium, chloride, total CO_2 (bicarbonate), creatinine, glucose, blood urea nitrogen or urea (if blood urea nitrogen test cannot be analyzed by the local laboratory), albumin, calcium total, magnesium total, inorganic phosphorus, alkaline phosphatase, alanine aminotransferase/glutamic-pyruvic transaminase, aspartate aminotransferase/glutamic-oxaloacetic transaminase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), uric acid

- C-reactive protein (CRP), ferritin

- Complete blood count (CBC) with differential

- 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, the pregnancy must be reported by contacting the Kite medical monitor for instructions. See Section 9.7 for pregnancy reporting.

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

Central laboratory analysis:

- Blood draws for PBMC (lymphocyte subsets, replication-competent retrovirus [RCR], and anti-CD19 CAR T-cell levels) and cytokine analysis will be performed at intervals outlined in the SOA. With each PBMC submission, also draw and include a CBC with differential to facilitate centrally the calculation of anti-CD19 CAR T-cell levels.

- Blood draws for lenzilumab PK will be performed at different intervals by study phase. Lenzilumab PK will be assessed with blood draws from a line not used for infusion of the related investigational product. In Phase 1, blood draws will occur **at baseline prior to lenzilumab infusion and then after completion of lenzilumab infusion** at 30 minutes and 1, 3, 6, 9, 12, and 24 hours **later**. Thereafter, blood draws for PK will coincide with cytokine draws from Days 1 to 7, specifically every 12 hours after infusion on Days 1 to 5, and then daily on Days 6 and 7. Further PK draws will occur at Weeks 2 and 4 in conjunction with other blood draws. In Phase 2, lenzilumab PK will be assessed **at baseline prior to lenzilumab infusion and then after completion of lenzilumab infusion** at 12 hours; thereafter, PK samples will be drawn twice daily from Day 1 to Day 5 and daily on Days 6 and 7 to coincide with cytokine blood draws. Further PK draws will occur at Weeks 2 and 4 in conjunction with other blood draws for these scheduled visits.

- CSF CCI [redacted] samples will also be collected and analyzed at the central laboratory as outlined in the SOA. CCI [redacted].

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]


CCI
CCI
CCI
CCI

CCI [redacted]

7.13. 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 for why the subject failed screening.

7.13.1. Screening

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

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 in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

The following assessments/procedures are to be completed during the screening period at the time points outlined in the SOA:

- Medical history and disease assessment
- Physical examination including height and weight
- Subjects with symptoms of CNS malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical examination will have an LP for examination of CSF and for assessment of opening pressure.
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- ECOG performance status
- Neurological assessment including ICE

- ECG
- ECHO for left ventricular ejection fraction and pericardial effusion assessment (an ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility)
- Imaging studies
  - Brain MRI
  - Baseline PET-CT of the neck, chest, abdomen, and pelvis
    - PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility.
    - If PET-CT is performed > 28 days prior to the initiation of lymphodepleting chemotherapy or if subject receives any anticancer therapy between screening and lymphodepleting chemotherapy, the scans must be repeated to establish a new baseline. PET-CT should be performed as close to enrollment as possible.

[redacted]

- Tuberculosis screening in relevant subjects based on medical history as per Section 7.3
- Laboratory tests
  - Chemistry panel
  - CBC with differential
  - β-human chorionic gonadotrophin pregnancy test (serum or urine) for all women of childbearing potential
  - Blood draw for RCR
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history

[redacted]

- Lumbar puncture for collection of CSF samples to be performed after eligibility confirmed and prior to start of lymphodepleting chemotherapy

7.13.2. Rescreening

Subjects who are unable to complete or meet the eligibility criteria during the 28-day screening period will be permitted to rescreen 1 time. Subjects will retain the same subject ID number assigned at the original screening. If rescreening occurs within 28 days of the signing of the

original informed consent, only the procedure(s)/assessment(s) that did not originally meet the eligibility criteria needs 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 signing of the original informed consent, subjects must be reconsented and repeat all screening procedures/assessments.

7.13.3. 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.

Before leukapheresis commences, the following 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 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.

Once 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:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Laboratory tests (to be drawn prior to leukapheresis, on the day of or day before leukapheresis)
  - Chemistry panel with LDH
  - CBC with differential
  - CRP and ferritin; if CRP is ≥ 100 mg/L, a call must be made to the Kite medical monitor before proceeding with lymphodepleting chemotherapy
  - Anti-CD19 CAR T cells
  - Lymphocyte subsets
  - Cytokine levels

- Leukapheresis
- AE/SAE reporting
- Concomitant medications documentation

CCI [redacted]

[redacted]

[redacted]

7.13.5. Lymphodepleting Chemotherapy Period

If any screening assessments or procedures are repeated between screening and the start of lymphodepleting chemotherapy and results are outside the eligibility criteria (Section 5), contact the Kite medical monitor for approval prior to proceeding with lymphodepleting chemotherapy.

The investigational product (axicabtagene ciloleucel) must be available before initiation of lymphodepleting chemotherapy.

7.13.5.1. Requirements for Initiating Lymphodepleting Chemotherapy

Administration of anti-CD19 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 a malignancy. Lymphodepleting chemotherapy and axicabtagene ciloleucel infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed.

If any of the following criteria are met prior to initiation of lymphodepleting chemotherapy, then the workup listed in Section 7.13.6.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of lymphodepleting chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of lymphodepleting chemotherapy
- White blood cell (WBC) count or WBC differential that is suggestive of infectious process and is observed between enrollment and the initiation of lymphodepleting chemotherapy (eg WBC > 20,000/μL, 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 lymphodepleting chemotherapy and the results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with lymphodepleting chemotherapy.

- Complete history and physical examination, including head, ears, eyes, nose, and throat examination, 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 known or suspected infection within 48 hours before lymphodepleting chemotherapy (prophylactic use of antimicrobials is allowed).

- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.

- If the 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 and in consultation with infectious disease service (if applicable).

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

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

7.13.5.2. Lymphodepleting Chemotherapy Administration

The following procedures will be completed during Day -5 to Day -3 at the time points outlined in the SOA:

- Physical Examination

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

- Laboratory tests (to be drawn prior to chemotherapy)

  — Chemistry panel

  — CBC with differential

- Fludarabine and cyclophosphamide administration
- AE/SAE reporting
- Concomitant medications documentation

7.13.6. Investigational Products Treatment Period

7.13.6.1. Requirements for Initiating Lenzilumab and Axicabtagene Ciloleucel Infusion

If any of the following criteria are met prior to the initiation of lenzilumab or axicabtagene ciloleucel infusion on Day 0, then the workup listed in Section 7.13.6.3 must be performed to determine the potential cause if there is no identified source of infection.

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

  Additionally: If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and the 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 lymphodepleting chemotherapy)
- Complete history and physical examination including head, ears, eyes, nose, and throat examination, 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 infusion (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 (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 administration of sequenced therapy.

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

7.13.6.2. Monitoring After Axicabtagene Ciloleucel Infusion

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility followed by daily monitoring at a healthcare facility for at least 7 days unless otherwise required by country regulatory agencies to monitor for signs and symptoms of CRS and neurologic toxicities. Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic toxicities in the hospital setting, if deemed appropriate by the investigator.

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

Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms, such as fever, dyspnea, confusion, aphasia, dysphagia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

During this period, the following procedures will be completed at the time points outlined in the SOA:

- Neurological assessment by ICE {Lee 2019}. ICE will be administered before treatment with axicabtagene ciloleucel on Day 0, and then daily from Day 1 through the 7-day postinfusion monitoring period.

- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature, daily at a healthcare facility for at least 7 days

- Laboratory tests (before lenzilumab and axicabtagene ciloleucel infusion, and after as described in the SOA)

- Chemistry panel with LDH
- CBC with differential
- Lymphocyte subsets
- Cytokine levels
- Anti-CD19 CAR T cells
- RCR analysis
- Lenzilumab PK (refer to Section 7.11 for directions based on Phase 1 and Phase 2)

- Infusion of lenzilumab on Day 0 initiated at least 6 hours prior to axicabtagene ciloleucel
- Infusion of axicabtagene ciloleucel on Day 0
- Lumbar puncture for collection of CSF samples at Day 5 (± 3 days)
- [redacted]
- [redacted]
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurologic toxicities. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and for at least 7 days at a healthcare facility. In addition, lactate should be monitored as clinically indicated.

7.13.6.3. Requirements for Workup Potential Infectious and/or Inflammatory States

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

- Call Kite medical monitor
- Infectious disease service consult (if available)

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

Prior to proceeding with lymphodepleting chemotherapy and/or axicabtagene ciloleucel infusion, the above workup must not suggest the presence of an active infection and all requirements for lymphodepleting chemotherapy and/or axicabtagene ciloleucel infusion must be satisfied. If the axicabtagene ciloleucel infusion is delayed > 2 weeks following lymphodepleting chemotherapy, protocol guidelines should be followed regarding the need for repeat lymphodepleting chemotherapy.

If the above workup was triggered due to CRP > 100 mg/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.

7.13.7. Post-treatment Assessment Period

After completing axicabtagene ciloleucel infusion and completing the minimum 7-day observation period, 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 3 (± 1 week)

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

- Neurological assessment including ICE
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- **Bone marrow aspirate and biopsy as needed**
- Physical examination
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Laboratory tests
  - Chemistry panel
  - CBC with differential
  - β-human chorionic gonadotrophin pregnancy test (serum or urine) for all women of childbearing potential
  - Cytokine levels
  - Lymphocyte subsets
  - Anti-CD19 CAR T cells
  - RCR analysis
  - Lenzilumab PK
- Lumbar puncture with opening pressure for collection of CSF samples at Week 4 (± 3 days)
- AE/SAE reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

If a subject is admitted to the hospital during the 7-day observation period, discharged, and is subsequently re-admitted to the hospital with any axicabtagene ciloleucel-related AE(s), the following laboratory tests will be collected on the day of hospital re-admission and then weekly through and including on the day of discharge:

- PBMCs (anti-CD19 CAR T cells)

- Cytokines
- Lenzilumab PK

At any time during the post-treatment assessment period, if a subject progresses 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 survival, subsequent therapy, and disease outcomes in the long-term follow-up period. A PBMC (for anti-CD19 CAR T cells) and serum sample (for cytokine evaluation) should be collected at the time of progression, prior to starting any subsequent anticancer therapy.

CCI [redacted]

7.13.8. Long-term Follow-up Period

- All enrolled subjects will be followed in the long-term follow-up period for survival and disease status, if applicable. Subjects will begin the long-term follow-up period after they have completed the Month 3 visit of the post-treatment assessment period (whether they have responded to treatment or went straight to the Month 3 visit due to disease progression). Every 3 months (± 2 weeks) through Month 12
- Every 12 months (± 3 months) between Month 24 – 15 years

The following procedures will be completed for subjects who are enrolled and receive sequenced therapy at the time points outlined in the SOA:

- Physical examination
- PET-CT/Disease assessment through 12 months or until disease progression, whichever occurs first. If subject's disease has not progressed by Month 12, disease assessments will continue to be performed per institutional standard of care.
- Survival status
- Laboratory tests
  - CBC with differential
  - Lymphocyte subsets
  - Anti-CD19 CAR T-cell levels
  - RCR analysis
- Subsequent therapy for the treatment of NHL

- Refer to Sections 9.2 and 9.4 for targeted AE/SAE reporting
  - Including neurological, hematological, and autoimmune disorders, and infections and secondary malignancies
- Targeted concomitant medication documentation (for 12 months or until disease progression, whichever occurs first)
  - Including gammaglobulins, immunosuppressive drugs, anti-infectives, and vaccinations

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

All subjects, subjects who received an infusion of axicabtagene ciloleucel will be given the opportunity to transition to a separate LTFU study, KT-US-982-5968, after providing informed consent.

If a subject progresses in the long-term follow-up phase, the subject will continue to be followed for survival status and subsequent therapy for the treatment of NHL. A PBMC sample (for anti-CD19 CAR T cells) and serum (for cytokine evaluation) should be collected at the time of progression, prior to starting any subsequent anticancer therapy.

CCI [redacted]

Subjects who are enrolled, but do not receive axicabtagene ciloleucel treatment, will be followed only until the end of this study and will undergo the following assessments at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per standard of care
- AE/SAE reporting and concomitant medication documentation until 30 days after last procedure (eg, leukapheresis, lymphodepleting 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.

7.13.9. Retreatment

Subjects who achieve a partial response (PR) or complete response (CR) have an option to receive a second course of lymphodepleting chemotherapy and axicabtagene ciloleucel without lenzilumab under the following conditions:

- Subject had a documented PR or CR to sequenced therapy
- Subject's disease subsequently progresses
- CD19 tumor expression confirmed locally by immunohistochemistry or flow cytometry on a representative progression biopsy
- Subject would meet study eligibility requirements for treatment with axicabtagene ciloleucel, except regarding prior CD19 targeted therapy or prior CAR T cell therapy. Screening assessments should be repeated if clinically indicated, as determined by the investigator and Kite medical monitor, to confirm said eligibility.
- Subject has not received any subsequent therapy for the treatment of lymphoma
- Subject did not experience a DLT in Phase 1 or a comparable toxicity in Phase 2
- Toxicities related to lymphodepleting chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment
- Subject would not require additional leukapheresis for retreatment

The decision to administer retreatment should be made in consultation with the Kite medical monitor. Retreatment will be considered a subsequent therapy. Retreated subjects will follow the schedule of assessments as specified in section 7.14 during and after retreatment, excluding assessments solely related to lenzilumab. Further adjustments to the schedule of assessments must be discussed with the Kite medical monitor.

7.14. Summary of Scheduled Assessments

The SOA and the long-term follow-up assessments are provided in Table 3 and Table 4, respectively.

Table 3. Schedule of Assessments

Procedures	Screening	Enrollment / Leukapheresis	CCI	Lymphodepleting Chemotherapy Period			IP Admin	Post-treatment Intensive Monitoring Period												Post-treatment Follow-up		
				-5	-4	-3	0	1		2		3		4		5		6	7	Week 2	Week 4	Month 3
Day	Within 28 days of enrollment	Within ~5 days of eligibility confirmation						AM	PM	AM	PM	AM	PM	AM	PM	AM	PM			(± 2 days)	(± 3 days)	(± 1 week)
Medical history[2]	X																					
ECOG performance status	X																					
Neurological assessment including immune effector cell-associated encephalopathy score[3]	X						X	X		X		X		X		X		X	X	X	X	X
Electrocardiogram	X																					
Echocardiogram	X																					
CCI																						
CCI																						
Brain MRI	X																					
PET-CT/ disease assessment[6]	X																				X	X
Physical examination	X			X			X	X		X		X		X		X		X	X	X	X	X
Vital signs (BP, HR, O2 saturation, temperature)	X	X		X	X	X	X	X		X		X		X		X		X	X	X	X	X

Procedures	Screening	Enrollment / Leukapheresis	CCI	Lymphodepleting Chemotherapy Period			IP Admin	Post-treatment Intensive Monitoring Period												Post-treatment Follow-up		
Day	Within 28 days of enrollment	Within ~5 days of eligibility confirmation		-5	-4	-3	0	1 AM	1 PM	2 AM	2 PM	3 AM	3 PM	4 AM	4 PM	5 AM	5 PM	6	7	Week 2 (± 2 days)	Week 4 (± 3 days)	Month 3 (± 1 week)
Weight (plus height at screening)	X	X																				
Pregnancy test (serum or urine)	X	X[7]		X[7]																		X
CCI																						
Blood draw for chemistry panel	X	X		X	X	X	X	X		X		X		X		X		X	X	X	X	X
Blood draw for CBC with differential[8]	X	X		X	X	X	X[8]	X[8]		X		X[8]		X		X[8]		X	X[8]	X[8]	X[8]	X[8]
Serology (EU sites)[9]	X[9]	X[9]																				
Blood draw for C-reactive protein (CRP)/ferritin		X					X	X		X		X		X		X		X	X			
Blood draw for LDH		X					X	X		X		X		X		X		X	X	X	X	X
CCI																						
CCI																						
Blood draw for PBMCs[8,10]		X					X	X				X				X			X	X	X	X
Blood draw for lenzilumab PK[12]							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedures	Screening	Enrollment / Leukapheresis	CCI	Lymphodepleting Chemotherapy Period			IP Admin	Post-treatment Intensive Monitoring Period												Post-treatment Follow-up		
				-5	-4	-3	0	1		2		3		4		5		6	7	Week 2	Week 4	Month 3
Day	Within 28 days of enrollment	Within ~5 days of eligibility confirmation						AM	PM	AM	PM	AM	PM	AM	PM	AM	PM			(± 2 days)	(± 3 days)	(± 1 week)
Leukapheresis		X																				
CCI																						
Fludarabine/ Cyclophosphamide				X	X	X																
Axicabtagene ciloleucel infusion IV							X															
Lenzilumab infusion IV							X															
AEs/ Concomitant medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP, blood pressure; CBC, complete blood count; CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, heart rate; IP, investigational product; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; PET-CT, positron emission tomography-computed tomography; RCR, replication-competent retrovirus; IV, intravenous.

CCI

2. Tuberculosis testing should be performed in subjects with a history of tuberculosis and for those subjects at high risk for tuberculosis exposure related to medical history. Testing may include either the tuberculin skin test or interferon gamma release assay, at the investigators discretion, and must have been performed within 3 months of anticipated lenzilumab administration.
3. Perform scoring according to Appendix 3, as described in Section 7.5. Scoring should be continued daily during any period of Grade 2 or higher neurologic events as per Section 7.5.

CCI

5. As applicable per Section 7.8, bone marrow aspirate and biopsy **may** be performed **at the discretion of the investigator.** Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities after sequenced therapy (see Section 7.12).

6. PET-CT (neck, chest, abdomen, and pelvis)/disease assessment performed following last line of therapy (>28 days from enrollment) may be used for confirmation of eligibility. If PET-CT performed > 28 days prior to the initiation of lymphodepleting chemotherapy or if subject receives any anticancer therapy between screening and lymphodepleting chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. Baseline scans should be provided to the central imaging review for evaluation of disease burden.
7. Pregnancy test (serum or urine) for EU sites: A pregnancy test will be completed within 7 days prior to both leukapheresis and lymphodepleting chemotherapy for females of childbearing potential.
8. At the time of PBMC collection, collect CBC with differential for central submission to allow for a more rapid analysis of anti-CD19 CAR T-cell levels in the blood.
9. Viral testing for EU sites: A viral serologic tests (eg, HIV, Hepatitis B, and Hepatitis C) will be carried out per institution guidelines and EU regulations. Testing may be done within the 30 days prior to leukapheresis and/or on the day of leukapheresis.

CCI [redacted]

12. Lenzilumab pharmacokinetics will be assessed with blood draws from a line not used for infusion of the related investigational product. In Phase 1, blood draws will occur at **baseline**, 30 minutes and 1, 3, 6, 9, 12, and 24 hours after infusion of lenzilumab. Thereafter, blood draws will coincide with remaining cytokine blood draws from Days 1-7 and Weeks 2 and 4. In Phase 2, blood draws will occur at **baseline and at** 12 hours after infusion, before coinciding with remaining cytokine blood draws from Days 1-7 and Weeks 2 and 4. Please refer to Section 7.11 for further information.

Table 4. Schedule of Assessments (Long-term Follow-up Period)

Procedure	Long-term Follow-up Period [9] (Each visit calculated from Day 0)				
Visit Frequency	Month 6 (± 2 weeks)	Month 9 (± 2 weeks)	Month 12 (± 2 weeks)	Month 24 and Annually Thereafter (± 3 months)	At Time of Progression
Physical examination[1]	X	X	X		X
PET-CT/disease assessment[2]	X	X	X		
CCI					
Survival status	X	X	X	X	
Blood draw for CBC with differential [4]	X	X	X		X
Blood draw for PBMC[4]	X	X	X		X
Blood draw for RCR analysis [4,5]	X		X	X	
Targeted AE/SAEs [6]	X	X	X		
Targeted concomitant medication [7]	X	X	X		
Subsequent therapy for NHL[8]	X	X	X	X	X

Abbreviations: AE, adverse event; CBC, complete blood count; NHL, non-Hodgkin's lymphoma; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; SAE, serious adverse event; RCR, replication-competent retrovirus.

1. Physical examinations will continue through Month 12 and then can be performed as per institutional standard of care.
2. PET-CT scans/disease assessments will continue through Month 12 or until disease progression, whichever comes first. If subject's disease has not progressed by Month 12, disease assessments will continue to be performed per institutional standard of care.

CCI

4. Subjects will continue to provide samples for central analysis of CBC with differential and PBMC to allow for evaluation of lymphocyte subsets and anti-CD19 CAR T cells through Month 12. On days where PBMC is drawn, an RCR blood draw does not need to be performed separately.
5. RCR samples: Collected and measured at Months 3, 6, and 12, then collected yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.
6. Targeted AEs/SAEs will be collected for 12 months or until disease progression (whichever occurs first)
7. Targeted concomitant medications will be collected for 12 months or until disease progression (whichever occurs first)
8. Subsequent therapy administered after axicabtagene ciloleucel infusion for a subjects' disease, such as nonstudy specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, must be collected until the subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies. Subjects may be contacted by telephone to collect information about subsequent therapy for NHL and to assess survival status.
9. After completion of at least 6 months of assessments in the KT-US-471-0119 study, subjects who received an infusion of axicabtagene ciloleucel will be provided the opportunity to transition to a LTFU study (KT-US-982-5968) after providing signed informed consent to complete the remainder of their LTFU period.

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 investigational product, 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 from 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, publically 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 investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole or at any time prior to study completion.

8.1. Reasons for Removal From Treatment

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

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

8.2. Reasons for Removal From Study

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

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

9. SAFETY REPORTING

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or interventions for pre-existing conditions, such as elective cosmetic surgery, or medical procedures 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, B-cell lymphoma).

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

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.

9.2. Reporting of Adverse Events

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 lenzilumab and axicabtagene ciloleucel infusion are monitored and reported. After 3 months, targeted AEs, including, for example, neurological, hematological, autoimmune disorders, infections, and secondary malignancies, will be monitored and reported for 12 months after treatment with the sequenced therapy or until disease progression, whichever occurs first.

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

The investigator must address the following for AEs:

- Adverse event diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to investigational product, lymphodepleting chemotherapy, or study procedures
- Action taken

The AE grading scale used will be the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 to match the criteria used in Cohorts 1 and 2 of ZUMA-1. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program home page (http://ctep.cancer.gov). For neurologic events, in addition to grading by the CTCAE v4.03 investigator's should provide a narrative report of each incident, including onset, evolution of symptoms, treatment employed, and resolution, if any by the D28 visit. Cytokine release syndrome events will also be reported using the grading scale outlined in the IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) the investigational products (lenzilumab and/or axicabtagene ciloleucel), 2) lymphodepleting chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the eCRF. 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 eCRFs.

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 nonserious AEs ends at the time the new treatment is started.

9.2.1. Reporting Abnormal Laboratory Findings

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

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

- 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

9.3. Definition of Serious Adverse Events

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

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important 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 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; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded in the eCRF.

9.4. Reporting of Serious Adverse Events and Nonserious CRS Events Grade ≥ 3

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after the signing of the consent through 30 days after completing the final dose of lenzilumab or 3 months after the axicabtagene ciloleucel infusion, whichever is longer.

Once this follow-up period has been completed, only serious targeted AEs (eg, neurological, hematological, autoimmune disorders, infections, and secondary malignancies) observed by the investigator or reported by the subject will be reported for 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. For subjects who fail screening or are enrolled but do not receive either investigational product, the reporting period for SAEs ends 30 days after the last procedure (eg, screening procedure, leukapheresis, lymphodepleting chemotherapy).

Serious AEs that the investigator assesses as related to the investigational products, lenzilumab, and/or axicabtagene ciloleucel should be reported regardless of the study period.

All SAEs must be submitted to Kite via the eSAE system within 24 hours of the investigator's knowledge of the event. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the 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.

Progression of the malignancy during the study should not be reported as an SAE. Adverse events associated with disease progression may be reported as an SAE. If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy, lenzilumab, or axicabtagene ciloleucel, then the event leading to death must be recorded as an SAE with an NCI CTCAE of Grade 5.

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 preconditioning, and within 30 days of the last lenzilumab infusion or 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 lenzilumab and axicabtagene ciloleucel infusions requires expedited reporting within 24 hours only if it is considered related to treatment.

Following completion of KT-US-471-0119, any relevant information on ongoing SAEs must be submitted to Kite Pharma within 24 hours of the investigator's knowledge of the event using the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: PPD

9.5. Reporting Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying lymphoma should be recorded as SAEs with the preferred term "B-cell lymphoma" and must be reported immediately to the sponsor. Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. 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 on (eg, after autopsy). Deaths during the poststudy survival follow-up due to underlying cancer should be recorded only in the Survival Status section of the eCRF.

9.6. Diagnosis Versus Signs and Symptoms

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

9.7. Pregnancy and Lactation

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

Female subjects and female partners of male subjects are recommended to use highly effective contraception (method must achieve an annual failure rate of < 1%) for at least 6 months after lymphodepleting chemotherapy dosing or the administration of axicabtagene ciloleucel, whichever is longer. Male subjects are recommended to not father a child for at least 6 months after the lymphodepleting chemotherapy dosing or the administration of axicabtagene ciloleucel, whichever is longer. Refer to Appendix 2 for a complete list of highly effective contraception methods.

If a pregnancy occurs in either a female subject enrolled into the study or a female partner of a male subject within 6 months of completing lymphodepleting chemotherapy or the administration of axicabtagene ciloleucel, whichever is longer, the pregnancy must be reported to Gilead PVE (PPD or fax PPD using the pregnancy report form within 24 hours. Refer to Section 9 of the protocol (Safety Reporting) and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting. Information regarding the pregnancy and/or the outcome will be requested by the sponsor. The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and should be reported as described in Section 9.4 of the protocol (SAE Reporting). Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE (PPD or fax: PPD

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows: email: PPD and fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

If a lactation case occurs in a female in the study, report the lactation case to Gilead PVE (PPD using the lactation reporting form 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 pregnancy and lactation cases for 15 years after the administration of axicabtagene ciloleucel dosing.

9.8. Hospitalization and Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be SAEs:

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

9.9. Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding 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 in the eCRF.

9.10. Safety Review Team and Dose-limiting Toxicity

Phase 1

The SRT will be specifically chartered to review safety data during Phase 1 of the study and make recommendations on further study conduct in Phase 1 and progression to Phase 2 based on the incidence of DLTs with sequenced therapy, review of SAEs, and translational data.

Dose-limiting toxicity is defined as the following sequenced therapy-related events with onset within the first 28 days following axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 28 days from the day of cell transfer
- Any sequenced therapy-related AE requiring intubation, including Grade 4 encephalopathy requiring intubation for airway protection, is considered to be a DLT
- Any sequenced therapy-related Grade 5 event
- All other clinically significant Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following conditions which are not considered DLT's:
  - Encephalopathy that resolves to at worst Grade 1 within 2 weeks and to baseline within 4 weeks
  - Grade 3 fever
  - Myelosuppression (includes bleeding in the setting of platelet count $< 50 \times 10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia, and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above
  - Immediate hypersensitivity reactions occurring within 2 hours of cell or lenzilumab infusion that are reversible to Grade 2 or less within 24 hours of administration with standard therapy
  - Renal toxicity which requires dialysis for ≤ 7 days
  - Tumor lysis syndrome including associated manifestations attributable to tumor lysis syndrome (eg, electrolyte abnormalities, renal function, hyperuricemia)

- Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ Grade 2 within 14 days
- Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ Grade 3 within < 72 hours
- Grade 3 or 4 hypogammaglobulinemia
- Grade 3 nausea or anorexia

CRS will be graded according to a revised grading system {Lee 2014}, as described in the current axicabtagene ciloleucel IB. Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. If Grade 3 or 4 CRS per Lee 2014 is due to one of the exceptions above, the event will not be considered a DLT.

During Phase 1, approximately 3 to 12 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of the sequenced therapy.

Subjects in each cohort will be evaluated for DLTs within the first 30 days following the completion of axicabtagene ciloleucel infusions. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.6. The SRT will make recommendations based on the incidence of DLT and overall safety profile of sequenced therapy with lenzilumab and axicabtagene ciloleucel. If the subject incidence of DLT is ≤ 1 of 6 subjects in Cohort 1 and 2, the RP2D will be selected by the SRT and the study can proceed to Phase 2. This decision will be based on overall benefit/risk assessment of adding lenzilumab to the axicabtagene ciloleucel regimen and available translational data.

However, if 2 of the 6 enrolled subjects present with a protocol-defined DLT during Phase 1, the SRT may recommend enrolling additional subjects at the relevant cohorts for further safety review and translational assessment (up to 12 subjects in total).

If the subject incidence of DLT is > 2/6, > 3/9, or > 4/12 subjects, other lenzilumab dosing regimens may be explored. The same DLT rules apply as above.

Phase 2

The SRT will meet to review the interim analysis once a total of 14 subjects have been treated at the RP2D and have been followed for 28 days after treatment with sequenced therapy across Phase 1 and Phase 2. In addition, the SRT will review futility according to the statistical analysis plan as in Section 10.5.The SRT may meet more often as needed during Phase 2 of the study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

This study is designed to differentiate between a treatment that has a true event rate of 20% or less and a treatment with a true event rate of 45% or more. The hypothesis is that the Grade 2 or higher neurologic event rate related to sequenced therapy is significantly less than 45%. No hypothesis will be tested during Phase 1 of the study.

10.2. Study Endpoints

10.2.1. Primary

Phase 1: Incidence of DLT related to sequenced therapy with lenzilumab and axicabtagene ciloleucel

Phase 2: Incidence of Grade 2 or higher neurologic events within 28 days of axicabtagene ciloleucel administration

10.2.2. Secondary

The secondary endpoints include:

- The incidence AEs and SAEs, including CRS and neurologic events
- ORR: defined as the incidence of either a CR or a PR per the IWG Lugano Classification {Cheson 2014} as determined by the study investigators. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered nonresponders.
- CR rate: defined as the incidence of CR per the IWG Lugano Classification {Cheson 2014} as determined by the study investigators
- DOR: among subjects who experience an objective response, DOR is defined as the date of their first objective response to disease progression per the IWG Lugano Classification {Cheson 2014} as determined by study investigators or death from any cause. Subjects not meeting the criteria for disease progression or death by the analysis cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing. Subjects who receive additional anticancer therapy in the absence of documented disease progression will be censored at the last evaluable disease assessment prior to the additional therapy. Subjects who receive an SCT in the absence of documented disease progression will be censored at the last evaluable disease assessment prior to the date of the SCT. A sensitivity analysis will be conducted in which disease assessments obtained after the SCT while in axicabtagene ciloleucel-induced remission are included in the derivation of the DOR.

- PFS: defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the IWG Lugano Classification {Cheson 2014} as determined by study investigators or death from any cause. Subjects not meeting the criteria for disease progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive additional anticancer therapy in the absence of documented disease progression will be censored at the last evaluable disease assessment prior to the additional therapy. Subjects who receive an SCT in the absence of documented disease progression will be censored at the last evaluable disease assessment prior to the date of the SCT. A sensitivity analysis will be conducted in which disease assessments obtained after the SCT while in axicabtagene ciloleucel-induced remission are included in the derivation of PFS.

- OS: defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last date known as alive or the data cutoff date, whichever is earlier.

- Axicabtagene ciloleucel pharmacodynamics: levels of cytokines (including free GM-CSF) in blood

- Axicabtagene ciloleucel PK: levels of anti-CD19 CAR T cells in blood

CCI [redacted]

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately **3** to **36** subjects.

Up to 6 subjects in each cohort will be enrolled and treated in Phase 1 of this study.

If the study proceeds to the Phase 2, up to an additional 24 subjects will be enrolled at the RP2D for assessment of the reduction in the incidence of Grade 2 or higher neurologic event seen by adding lenzilumab to the axicabtagene ciloleucel regimen.

Simon's 2-stage design {Simon 1989} is used to calculate the sample size for the RP2D cohort. The null hypothesis that the true event rate is 45% will be tested against a 1-sided alternative. In the first stage, 14 subjects will be accrued and treated at the RP2D (including subjects treated at the RP2D under both Phase 1 and Phase 2). If there are 5 or more subjects with Grade 2 or above neurologic events in these 14 Stage 1 subjects, the study will be stopped

for futility at the discretion of the SRT. Otherwise, 16 additional subjects will be accrued and treated at the RP2D for a total of 30. The null hypothesis will be rejected if 8 or fewer subjects with Grade 2 or above neurologic events are observed in the 30 subjects. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true event rate is 20% or less. The probability of early stopping when the null hypothesis is true is 0.8328. CCI [redacted]

Table 5. Simon's Two-stage Design for RP2D[1] Cohort

Stages	Total Number of Subjects	Target Number of Subjects with Events
Stage 1	14	< 5
Stage 2	30	< 9

[1] RP2D: recommended phase 2 dose

All analyses for the incidence of Grade 2 or higher neurologic event in Phase 1 and Phase 2 portions of the study will be based on a primary objective analysis set consisting of all subjects who receive axicabtagene ciloleucel at a minimum dose of CCI anti-CD19 CAR T cells/kg CCI [redacted] and any dose of lenzilumab.

Inferential testing will be performed only for the primary endpoint in Phase 2 of the study.

10.4. Access to Individual Subject Treatment Assignments

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

10.5. Interim Analysis and Early Stopping Guidelines

During Phase 1, the SRT will review safety data after 3 and 6 (as needed) subjects have been followed for 28 days after their axicabtagene ciloleucel administration in each dose escalation cohort and will make recommendations on further study conduct and progression of the study as outlined in Section 9.10. At the conclusion of dose escalation, the SRT will determine the RP2D and conversion to Phase 2.

During Phase 2, the SRT will assess safety and futility through an interim analysis once 14 subjects are enrolled and treated with axicabtagene ciloleucel at a minimum dose of 1.6×10^6 anti-CD19 CAR T cells/kg CCI [redacted] and lenzilumab at the RP2D (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion, and have had the opportunity to be followed for 28 days after the axicabtagene ciloleucel dose. According to Simon's 2-stage design, if there are 5 or more subjects with events in the 14 Stage 1 subjects, the study will be stopped at the discretion of the SRT. This timing will coincide with an interim analysis.

10.6. Analysis Subsets

- Full analysis set (FAS): The full analysis set will consist of all enrolled subjects and will be used for the summary of subject disposition.

- Primary objective analysis set: The primary objective analysis set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a minimum dose of 1.6 x 10^6 anti-CD19 CAR T cells/kg [redacted] and any dose of lenzilumab at the RP2D (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion. This analysis set will be used for the primary endpoint analysis.

- Modified intent-to-treat set: The modified intent-to-treat set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a minimum dose of [redacted] anti-CD19 CAR T cells/kg [redacted] and any dose of lenzilumab at the RP2D (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion. This analysis set will be used for all efficacy analyses.

- Safety set: The safety set is defined as all subjects treated with any dose of axicabtagene ciloleucel and/or any dose of lenzilumab. This analysis set will be used for all safety analyses except for the primary endpoint analysis.

- Sensitivity analysis for some key secondary endpoints (eg, incidence rate by severity of CRS, incidence rate by severity of neurologic events) may be performed based on the primary objective analysis set.

DLT evaluable set (Phase 1 only): defined for each dosing cohort in Phase 1, will include subjects treated in the Phase 1 dosing cohort who:

- Received the target dose of lenzilumab and axicabtagene ciloleucel and were followed for at least 28 days after the anti-CD19 CAR T cell infusion; or

- Received a dose of lenzilumab lower than the target for that cohort and experienced a DLT during the 28-day postinfusion period.

Depending on the dosing cohort and results of the Phase 1 portion of the study, lenzilumab may be:

- Administered as a single IV infusion at a target dose 600 mg on Day 0 prior to administration of 2 x 10^6 anti-CD19 CAR T cells/kg (± 20%) [redacted] or

- Administered as a single IV infusion at a target dose 1800 mg on Day 0 prior to administration of 2 x 10^6 anti-CD19 CAR T cells/kg (± 20%); or

- If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each cohort.

10.7. Planned Method of Analysis

The primary analysis will be performed after 30 subjects in the primary objective analysis set have had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The final analysis will occur when all subjects have completed the study. Additional analyses of safety and efficacy may occur at any time after the primary analysis.

10.7.1. Grade 2 or Higher Neurologic Events Rate

The primary endpoint of incidence of Grade 2 or higher neurologic event for all analyses (futility, interim, and primary) will be based on investigator review of neurologic assessments, signs and symptoms in the primary objective analysis set. The incidence of Grade 2 or higher neurologic events and the exact 2-sided 95% confidence interval will be generated. An exact binomial test will be used to compare the observed event rate to an event rate of 45%.

10.7.2. Safety

Subject incidence rates of AEs including all, serious, fatal, and NCI CTCAE version 4.03 Grade 3 or higher, and treatment-related AEs reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Identified and potential risks of axicabtagene ciloleucel and lenzilumab infusions will be summarized. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through long-term follow-up and treatment-related SAEs will be provided.

10.7.3. Objective Response Rate

The incidence of ORR and exact 2-sided 95% confidence intervals will be generated.

10.7.4. Complete Response Rate

The incidence of CR rate and exact 2-sided 95% confidence intervals will be generated.

10.7.5. Duration of Response

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for DOR. Estimates of the proportion of subjects alive and in response at 3-month intervals will be provided.

10.7.6. Progression-free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and in response at 3-month intervals will be provided.

10.7.7. Overall Survival

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

CCI [redacted]

[redacted]

10.7.9. Long-term Data Analysis

All subjects will be followed for survival status for up to 15 years after receiving axicabtagene ciloleucel. LTFU data analysis will be performed on subjects in this study and after transition to the KT-US-982-5968 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.

11. REGULATORY OBLIGATIONS

11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF, and any additional subject or trial information such as subject recruitment materials must be submitted to each sites respective IRB/IEC for approval. Once 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

Subject confidentiality must be contained for 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 according to local laws and regulations

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

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

11.3. Investigator Signatory Obligations

Each 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
- Participated in the study and enrolled a high number of eligible subjects

12. PROTOCOL AMENDMENTS AND TERMINATION

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

Both Kite 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 contract research organization with a copy of the correspondence.

Kite reserves the unilateral right, at is 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 who are 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. Example of such source documents may include, but are not limited to, hospital records and subject charts; laboratory, pharmacy, radiology and records; subject diaries; microfiches; correspondence; and death registries. Case report form entries may be considered as source data if the site of the original data collection is not available. However, use of the eCRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralize 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 a minimum the following:

- Subject content including ICFs and subject ID lists
- Protocols and protocol amendments, IB, copies of prestudy 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 eCRFs 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.

14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contact, monitors, auditors, and 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 eCRF 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 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 eCRF system. All entries must be completed in English and concomitant medications should be identified by tradenames. For further details surrounding the completion of eCRFs, please refer to the eCRF completion guidelines.

15. PUBLICATION

Authorship of publications from data generated in study ZUMA-19 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals as outlined in the International Committee of Medical Journal Editors {International Committee of Medical Journal Editors 2018}, which states that authorship should be based on the following criteria:

- 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, collecting data, or general supervising 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 between the institution, principal investigation, and Kite or its delegate will outline the requirements for publication review.

16. COMPENSATION

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

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18. APPENDICES

Appendix 1. International Working Group Lugano Classification {Cheson 2014}

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

Complete Remission:

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

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

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

Complete Radiologic Response for Computed Tomography-Based Response

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

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

Partial Remission:

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

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

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

  Note:

  — At interim, these findings suggest responding disease.

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

- No new sites of disease should be observed

- Residual uptake is higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake is compatible with reactive changes from chemotherapy allowed).

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

Partial Radiologic Response for Computed Tomography-Based Response

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

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

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

  — When no longer visible, 0 x 0 mm

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

- Absent/normal, regressed, but no increase of nonmeasured lesions

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

- No new sites of disease should be observed

Stable Disease:

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

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

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

Stable Radiologic Disease for Computed Tomography-Based Response

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

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

Progressive Disease:

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

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

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

Progressive Radiologic Disease for Computed Tomography-Based Response

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

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

Appendix 2. Birth Control Methods Which May Be Considered as Highly Effective

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

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation[2]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[2]:
  - Oral
  - Injectable
  - Implantable[3]
- Intrauterine device[3]
- Intrauterine hormone-releasing system[3]
- Bilateral tubal occlusion[3]
- Vasectomized partner [3,4]
- Sexual abstinence[5]

1 2014 clinical trial facilitation and coordination group contraception guidance
2 Hormonal contraception may be susceptible to interaction with the investigational product, which may reduce the efficacy of the contraception method.
3 Contraception methods that in the context of this guidance are considered to have low user dependency.
4 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
5 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Appendix 3. Immune Effector Cell-associated Encephalopathy (ICE) Score

ICE[1]
Orientation: orientation to year, month, city, hospital: 4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
Writing: ability to write a standard sentence (eg, "Our national bird is thebald eagle"): 1 point
Attention: ability to count backwards from 100 by 10: 1 point

[1] ICE score as developed by the American Society for Transplantation and Cellular Therapy consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells (2019) {Lee 2019}.

Appendix 4. European regulatory agency requirements

The post-infusion monitoring of subjects (described in Section 6.2.2.3 and Section 7.13.6.2 of this protocol) will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 3, column "IP Admin, D1 to 7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with CRP, blood draw for CBC w/differential, and neurological assessment (see Section 7.11). Any observed toxicity will be managed according to Section 6.1.9 of this protocol.