CLINICAL STUDY PROTOCOL

A PHASE 1/2 MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL IN COMBINATION WITH UTOMILUMAB IN SUBJECTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA (ZUMA-11)

Protocol Title:	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Utomilumab in Subjects with Relapsed/Refractory Large B-Cell Lymphoma
Protocol Number:	KTE-C19-111
USAN/INN:	Axicabtagene ciloleucel Utomilumab
Company Code:	KTE-C19 PF-05082566
IND Number:	016278
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PROTOCOL SYNOPSIS

Title: A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Utomilumab in Subjects with Relapsed/Refractory Large B-cell Lymphoma

Indication: For the treatment of adult subjects with relapsed/refractory large B-cell lymphoma

Study Design: This is a Phase 1/2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with utomilumab administration in subjects with relapsed/refractory large B-cell lymphoma. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

During Phase 1, up to 36 subjects with refractory large B-cell lymphoma will be enrolled in a 3+3 design in up to 6 of 10 possible cohorts to evaluate the safety of axicabtagene ciloleucel and utomilumab combination regimens. Axicabtagene ciloleucel will be administered as a single dose, and utomilumab will be administered at escalating doses. Subjects will be enrolled and treated one at a time during the Phase 1 portion of the study. Subject treatment with axicabtagene ciloleucel will be staggered by at least 2 weeks. The Phase 1 cohorts and utomilumab regimens administered are outlined in the following table.

Dose Level*	Cohort	First Utomilumab Administration
10 mg	1	Day 1
	1A	Day 21
30 mg	2	Day 1
	2A	Day 21
100 mg	3	Day 1
	3A	Day 21
200 mg	4	Day 1
	4A	Day 21
400 mg	5	Day 1
	5A	Day 21

* Utomilumab doses represent total doses (10 mg, 30 mg, 100 mg, 200 mg, and 400 mg) and will be administered Q4W for 6 months or until progressive disease (PD), whichever comes first.

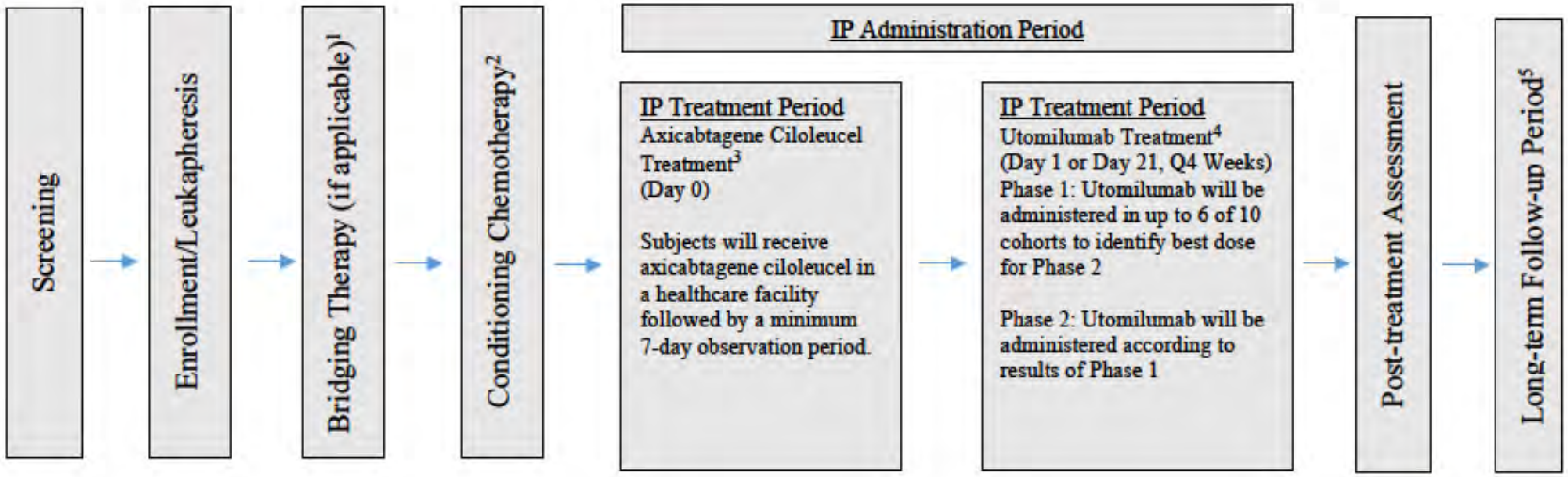
	A safety review team (SRT) that is internal to the study sponsor and at least one Phase 1 investigator will review safety data after all subjects in each Phase 1 cohort have had the opportunity to complete the dose-limiting toxicities (DLT) window. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 5 and outlined in Section 9.10. In Phase 2, approximately 24 subjects will be enrolled to receive treatment with axicabtagene ciloleucel and utomilumab based on the dose/regimen selected to move forward from the Phase 1 portion of the study as recommended by the SRT. Independent of the cohort or phase of the study, each subject will proceed through the following study periods: • Screening • Enrollment/Leukapheresis • Bridging therapy; if applicable • Conditioning chemotherapy • Investigational product treatment (axicabtagene ciloleucel and utomilumab) • Post-treatment assessment • Long-term follow-up (LTFU) For study requirement details assigned to each study period, refer to the schedule of assessments (SOAs) and Section 7. A study schema is provided in Figure 1.
Study Objectives:	Primary objective: • The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel in combination with utomilumab and to identify the most appropriate dose and timing of utomilumab to carry forward into Phase 2. • The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and utomilumab, as measured by complete response (CR) rate, in subjects with relapsed/refractory large B-cell lymphoma. Secondary objectives: • Secondary objectives for Phase 1 and Phase 2 will include assessing the safety and tolerability of axicabtagene ciloleucel and utomilumab, additional efficacy endpoints, and levels of axicabtagene ciloleucel in blood (pharmacokinetics [PK]) and levels of cytokines in serum.

Hypothesis:	No formal hypothesis will be tested in the study. The Phase 2 portion of the study is designed to estimate the true CR rate in subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel followed by utomilumab.
Primary Endpoints:	• Phase 1: Incidence of adverse events defined as DLTs • Phase 2: Complete response rate per the Lugano Classification {Cheson 2014}, (refer to Appendix 2), as determined by study investigators
Secondary Endpoint(s):	Phase 1 and Phase 2: • Objective response rate (CR + partial response [PR]) per the Lugano Classification {Cheson 2014}, as determined by study investigators • Duration of response • Progression-free Survival per the Lugano Classification {Cheson 2014}, as determined by study investigators • Overall survival (OS) • Incidence of adverse events and clinically significant changes in safety lab values • PK: Levels of axicabtagene ciloleucel in blood • Pharmacodynamics: Levels of cytokines in serum
Sample Size:	Approximately 3 to 60 subjects Phase 1: approximately 3 to 36 subjects Phase 2: approximately 24 subjects
Study Eligibility:	Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria.
Treatment:	Conditioning chemotherapy treatment: • A conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day will be administered x 3 days prior to axicabtagene ciloleucel infusion. Refer to Section 6 for chemotherapy treatment details.

	Bridging therapy period, if applicable: • Non-chemotherapy bridging therapy will be administered at the discretion of the investigator. For subjects receiving bridging therapy, refer to Section 6 for bridging therapy details. Investigational product(s): • Axicabtagene ciloleucel treatment consists of a single infusion of chimeric antigen receptor (CAR) transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg. Refer to Section 6 and Section 7.8 for treatment details. • Utomilumab treatment consists of an intravenous infusion started on either study Day 1 or study Day 21 and continuing Q4W for 6 months or until PD, whichever comes first. In the Phase 1 portion of the study, the doses of utomilumab administered will be 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg. Additional axicabtagene ciloleucel and utomilumab regimens may be explored in Phase 1 at the recommendation of the SRT. The axicabtagene ciloleucel and utomilumab treatment in Phase 2 will follow the dosing regimen with the best overall benefit/risk profile tested in Phase 1 as determined by the safety review team (see Figure 5). Subjects who receive axicabtagene ciloleucel treatment, which consists of a single infusion of CAR transduced autologous T cells administered intravenously on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (maximum 2 x 10^8 anti-CD19 CAR T cells) and at least one dose of utomilumab, will be considered evaluable in the efficacy set.
Procedures:	As outlined in the schedule of assessments (SOAs), subjects will undergo the following procedures: collection of informed consent and medical history, including Eastern Cooperative Oncology Group (ECOG) performance status. Subjects will also undergo blood draws for the following: • Local evaluation: complete blood count (CBC), chemistry panels, C-reactive protein, and pregnancy test (if applicable). • Central evaluation: CBC with differential, PK assessments (utomilumab and axicabtagene ciloleucel), pharmacodynamic assessment (cytokines), utomilumab anti-drug antibodies (ADA), replication-competent retrovirus (RCR), and lymphocyte subsets (B-cell recovery).

	Subjects will also undergo electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography-computed tomography (PET-CT), lumbar puncture (for cerebrospinal fluid [CSF] collection), CCI [redacted] Routinely throughout the conduct of the study, all subjects will be asked to report concomitant therapies, adverse events, and subsequent lymphoma therapy. Subjects will also undergo routine disease assessments as outlined in the SOA. For details for all study requirements, refer to Section 7 and the SOA.
Study Review Team (SRT):	An internal safety review team (SRT), comprising the study sponsor and at least one Phase 1 investigator, will review the safety data following the accrual and completion of the DLT assessment period of each Phase 1 cohort and make recommendations on further study conduct of Phase 1 and progression to Phase 2. The SRT will additionally meet on at least 1 occasion during the Phase 2 portion of the study after 6 subjects have completed their 1-month disease assessment. The SRT will review safety and efficacy data and will be chartered to make trial conduct recommendations based on an analysis of benefit/risk ratio. Refer to Section 9.10.
Statistical Considerations:	The primary endpoint for the Phase 1 portion of the study is the incidence of DLTs. The primary endpoint for the Phase 2 portion of the study is complete response rate per the Lugano Classification {Cheson 2014} as determined by the study investigators. This study utilizes a single-arm design to estimate the true complete response rate in subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel and utomilumab. With a total sample size of approximately 27 subjects at any given dosing schedule, of which at least 3 subjects will have been treated in the Phase 1 portion, an observed CR rate of 70% will yield an exact 95% confidence interval (CI) of (50%, 86%). This target CR rate, and the lower limit of the 70% CI for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with relapsed/refractory LBCL over existing therapies.

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



1 Non-chemotherapy bridging therapy will be administered at the discretion of the investigator. For subjects receiving bridging therapy, refer to Section 6.1.2 for bridging therapy details.
2 Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.
3 Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (maximum 2 x 10^8 anti-CD19 CAR T cells).
4 Utomilumab treatment consists of an intravenous infusion started on Day 1 or Day 21 and continuing Q4 weeks for 6 months or until PD, whichever comes first. The SRT will make recommendations on further study conduct of Phase 1. Additional axicabtagene ciloleucel and utomilumab regimens may be explored in Phase 1.
5 After the end of KTE-C19-111, subjects who received an infusion of axicabtagene ciloleucel and utomilumab will complete the remainder of the 15-year follow-up assessments in a separate Long-term Follow-up study, KT-US-982-5968.

Utomilumab treatment in Phase 2 will follow the dosing regimen from Phase 1 agreed upon by the study sponsors and the SRT.
Abbreviations: IP, investigational product.

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ABC	Activated B cell
ADA	Anti-drug antibody
AE	Adverse event
AICD	Activation induced cell death
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CAR	Chimeric antigen receptor
CBC	Complete blood count
C_{eff}	Efficacious concentration
CI	Confidence Interval
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DORR	Duration retreatment response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
FL	Follicular lymphoma
GCB	Germinal center B cell

GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
HEENT	Head, eye, ear, nose, and throat
HGBCL	High-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification
IF	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IP	Investigational product
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAP	Mitogen activated protein
MCP	Monocyte chemoattractant protein
MIP	Macrophage inflammatory protein
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
Nab	Neutralizing antibody
NCI	National Cancer Institute
NE	Neurologic event
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	Non-Hodgkin lymphoma
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography–computed tomography

PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
qPCR	Quantitative polymerase chain reaction
RCR	Replication-competent retrovirus
SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplant
SD	Stable disease
SOA	Schedule of assessment
SOC	Standard of care
SRT	Safety review team
TEAE	Treatment-emergent adverse event
TFL	Transformed follicular lymphoma
TGI	Tumor growth inhibition
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
ULN	Upper limit of normal
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

- Phase 1: To evaluate the safety of axicabtagene ciloleucel in combination with utomilumab and to identify the most appropriate dose and timing of utomilumab to carry forward into Phase 2
- Phase 2: To evaluate the efficacy of axicabtagene ciloleucel and utomilumab, as measured by complete response rate, in subjects with relapsed/refractory large B-cell lymphoma

1.2. Secondary Objective(s)

- Phase 1 and Phase 2: To assess the safety and tolerability of axicabtagene ciloleucel and utomilumab, additional efficacy endpoints, and levels of axicabtagene ciloleucel in blood (pharmacokinetics [PK]) and levels of cytokines in serum (pharmacodynamics)

CCI [redacted]

2. DISEASE BACKGROUND AND RATIONALE

2.1. Disease Background

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes, or natural killer (NK) cells. In the United States, B-cell lymphomas represent 80% to 85% of cases reported. In 2018, it is estimated that there will be approximately 74,680 new cases of NHL and over 19,000 deaths related to the disease. NHL is the most prevalent hematological malignancy and is the seventh most common type of cancer among men and women and accounts for 4.3% of all new cancer cases and 3% of deaths related to cancer {Noone 2017}.

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% of NHL cases. There are approximately 22,000 new diagnoses of DLBCL in the United States each year. In the past 2 decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of chemotherapy and immunotherapy. The addition of rituximab into combination therapies for DLBCL has greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL still have a particularly dire prognosis {Flowers 2010}.

SCHOLAR-1, a large multicenter, patient-level retrospective study, examined outcomes of refractory DLBCL 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 or stable disease 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 (ASCT). The study highlighted the poor prognosis of patients affected with refractory DLBCL, finding 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}.

2.2. Axicabtagene Ciloleucel

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 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 anti-human CD19 single-chain variable region fragment (scFv) derived from the monoclonal antibody FMC63; 2) the transmembrane co-stimulatory 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

co-stimulatory domains activate a downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector function.

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, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma (FL) {YESCARTA 2017}.

FDA approval was based on ZUMA-1, a single-arm multicenter trial of 108 adult subjects with relapsed or refractory aggressive large B-cell NHL. Of the 101 subjects evaluated for efficacy, the ORR was 72%, with a CR rate of 51%. The median duration of response (DOR) was longer in subjects with a best overall response of CR compared with those who achieved a best overall response of partial response (PR) (not estimable vs 2.1 months, respectively) {YESCARTA 2017}. The most common Grade 3 or higher adverse events (AEs; incidence of $\geq$ 10%) were fever, cytokine release syndrome (CRS), encephalopathy, infections (pathogen unspecified), hypotension, and hypoxia. Serious adverse reactions occurred in 52% of subjects and included, but were not limited to, encephalopathy, fever, febrile neutropenia, and serious infections. Fatal cases of CRS and neurologic toxicity occurred. FDA approved axicabtagene ciloleucel with a Risk Evaluation and Mitigation Strategy {YESCARTA 2017}.

The dose of axicabtagene ciloleucel is a single intravenous (IV) infusion with a target of 2×10^6 CAR-positive viable T cells per kg body weight (maximum 2×10^8 cells), preceded by cyclophosphamide and fludarabine lymphodepleting chemotherapy {YESCARTA 2017}. Additional details regarding the mechanism of action and clinical results of axicabtagene ciloleucel can be found in the most current version of the axicabtagene ciloleucel Investigator's Brochure (IB).

2.3. Prior Anti-CD19 CAR T-cell Study Design

The design and rationale of this study is in part derived from prior experience with axicabtagene ciloleucel on other Kite Pharma, Inc., (hereafter referred to as Kite or Kite Pharma) sponsored studies, including ZUMA-1, and on a single-center study conducted at the National Cancer Institute (NCI). See the most current version of the axicabtagene ciloleucel IB for details.

2.4. Utomilumab

The inducible co-stimulatory receptor 4-1BB (CD137 or tumor necrosis factor [TNF] superfamily 9) is a critical mediator of immune responses, and it is expressed on subsets of activated immune cells, including T cells {Wang 2009}. Its ligand, 4-1BBL, is expressed on activated antigen-presenting cells, and through 4-1BB engagement, it triggers downstream intracellular signaling through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and mitogen activated protein (MAP) kinase pathways that promote cellular proliferation, survival, and cytokine production {Croft 2009}. For these reasons, 4-1BB is an attractive immunotherapy target.

Utomilumab (company code: PF-05082566) is a highly selective, fully human 4-1BB IgG2 monoclonal antibody (mAb) that binds as an agonist to the human 4-1BB with nanomolar affinity. In preclinical studies, utomilumab activated the NF-kB pathway and induced downstream cytokine production in engineered cell lines and primary lymphocytes. In addition, utomilumab promoted human leukocyte proliferation in a model of human peripheral blood mononuclear cell (PBMC) engraftment and inhibited tumor growth in xenograft tumor models in which human PBMC had been co-engrafted. Utomilumab may, therefore, enhance the immune response against tumors {Fisher 2012} (refer to PF 05082566 IB).

2.4.1. Summary of Clinical Studies for Utomilumab

Clinical experience to date with utomilumab is summarized in Table 1. As of July 2017, PF-05082566 has been administered to a total of 390 subjects. Study B1641001 is a Phase 1 open-label, multicenter, dose escalation study of PF-05082566 as a single agent (Portion A) in subjects with relapsed solid tumors or relapsed or refractory B-cell lymphoma or in combination with rituximab (Portion B) in subjects with relapsed or refractory CD20 positive NHL (refer to PF-05082566 IB) {Gopal 2015, Segal 2018}. PF-5082566 doses ranged from 0.006 mg/kg to 10 mg/kg administered intravenously (IV) once every 28 days. The regimen was well tolerated with the most frequently observed treatment-related, treatment-emergent adverse event (TEAE) in Portion A being fatigue (14.0%). Treatment-related TEAEs were mostly Grade 1 or Grade 2 with only 4 Grade 3/4 AEs reported (colitis, diarrhea, fatigue, hyperbilirubinemia, and hyponatremia). The most frequently observed treatment-related TEAEs in Portion B with 66 subjects were infusion-related reaction (21.2%) and fatigue (19.7%). All of the infusion reactions were associated with rituximab infusion. PF-05082566-related TEAEs were either Grade 1 or Grade 2 in severity. Grade 3/4 AEs were reported in 6 subjects in combination with rituximab only: infusion-related reaction and neutropenia (2 subjects each) and decreased lymphocyte and neutrophil counts (1 subject each). There were no dose-limiting toxicities (DLTs). PF-05082566 is now considered to be safe up to doses of 10 mg/kg, equivalent to approximately 700 mg in a 70-kg subject, as a monotherapy or in combination with rituximab (375 mg/m^2). Thus, the proposed starting dose of 10 mg total dose for this protocol renders a margin of safety of at least 70-fold relative to historical safety data.

Study B1641003 is a Phase 1 open-label, multicenter, dose escalation study of PF-05082566 administered in combination with pembrolizumab (an anti PD-1 mAb) in adult subjects with advanced solid malignancies. Enrollment of subjects into the dose escalation phase of the study is complete, with 23 subjects enrolled at PF-05082566 doses ranging from 0.45 mg/kg to 5.0 mg/kg administered IV concurrently with pembrolizumab at 2 mg/kg once every 21 days. Treatment-related TEAEs were mostly Grade 1 or Grade 2. There were only 2 treatment-related (PF-05082566 and pembrolizumab) Grade 3 AEs reported in 2 subjects: adrenal insufficiency (no evidence of associated hypophysitis) and hypokalemia (1 subject each). No Grade 4 or Grade 5 treatment-related AEs were observed. This combination was well tolerated when the maximum administered dose of PF-05082566 was 5 mg/kg for this combination, roughly 350 mg in a 70-kg subject, and was deemed well tolerated with no DLTs observed in the study. Other combination strategies are also under investigation as shown in Table 1.

Table 1. Clinical Experience with Utomilumab

Protocol	Title	Subjects		Status
		Planned	Treated	
B1641001	A Phase 1 Study of PF 05082566 as a Single Agent in Patients with Advanced Cancer and in Combination with Rituximab in Patients with Non-Hodgkin's Lymphoma (NHL)	72-161	180	Ongoing
B1641003	A Phase 1 Study of the 4-1BB Agonist PF- 05082566 in Combination With the PD-1 Inhibitor MK-3475 in Patients with Advanced Solid Tumors	45-75	23	Completed
B1641004	A Phase 1b Study of PF-05082566 in Combination With Mogamulizumab (KW-0761) in Patients With Advanced Solid Tumors	70	24	Terminated
B9991004	A Phase 1b/2 Open-Label Study to Evaluate Safety, Clinical Activity, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination with Other Cancer Immunotherapies in Patients with Advanced Malignancies (Avelumab IB version 7, 31 March 2017)	317	153	Ongoing
B0601002	A Phase 1 Open Label, Dose Escalation Study of PF-04518600 as a Single Agent and in Combination with PF-05082566 in Patients with Selected Locally Advanced or Metastatic Carcinomas (PF-04518600 IB December 2016)	190	10	Ongoing

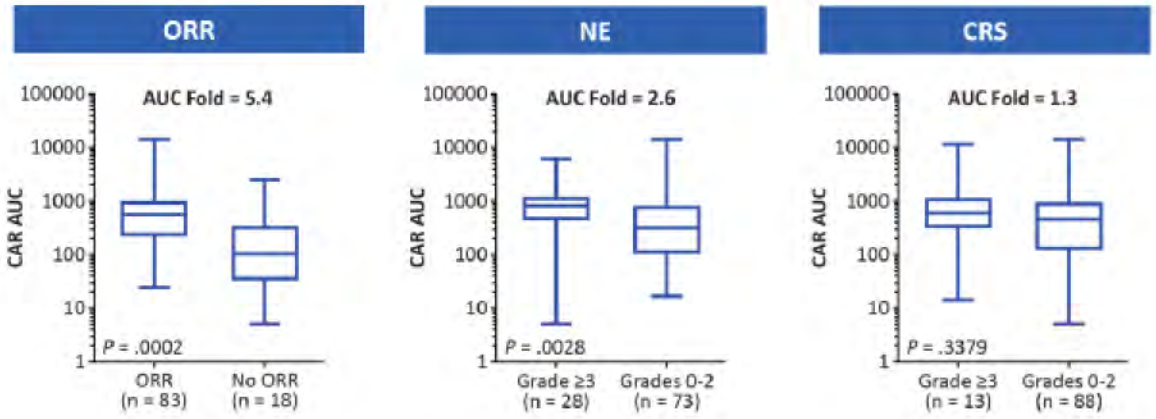
Abbreviations: IB, Investigator's Brochure.

2.5. Rationale for Combination Therapy

Previous clinical trial experience with axicabtagene ciloleucel in the same patient population (ZUMA-1) demonstrated an ORR of 82% and a CR rate of 58% at the updated analysis after median follow-up of 15.4 months {Neelapu 2017b}. Ongoing responses were seen in 42% of subjects, of which 40% were in CR. Among the 58% of subjects who were not in ongoing response at the 12-month follow-up, 18% of subjects demonstrated primary resistance to therapy (did not achieve PR or CR), and 40% of subjects achieved an objective response and later progressed or died {Neelapu 2017a}. Possible mechanisms of resistance to axicabtagene ciloleucel are hypothesized to be suboptimal CAR T-cell expansion {Neelapu 2017b}, an exclusionary tumor microenvironment {Rossi 2018}, and CD19 target antigen loss {Neelapu 2017a}.

Further, it was also observed in ZUMA-1 that 23/60 subjects with either a PR (11/35) or stable disease (SD) (12/25) at the first tumor assessment (1 month after axicabtagene ciloleucel administration) subsequently achieved CR up to 15 months after infusion without additional therapy {Neelapu 2017a}. In addition, peak expansion and area under the curve$_{0\text{-}28d}$ ($AUC_{0\text{-}28d}$) are associated with response {Neelapu 2017b} (Figure 2). Therefore, combination strategies that either increase proliferation, expansion, and persistence of CAR T cells or prevent activation-induced cell death (AICD) of CAR T cells may improve clinical outcomes seen with anti-CD19 CAR T-cell therapy.

Figure 2. **Expansion of CAR T Cells was Associated with Objective Response and Neurologic Events**



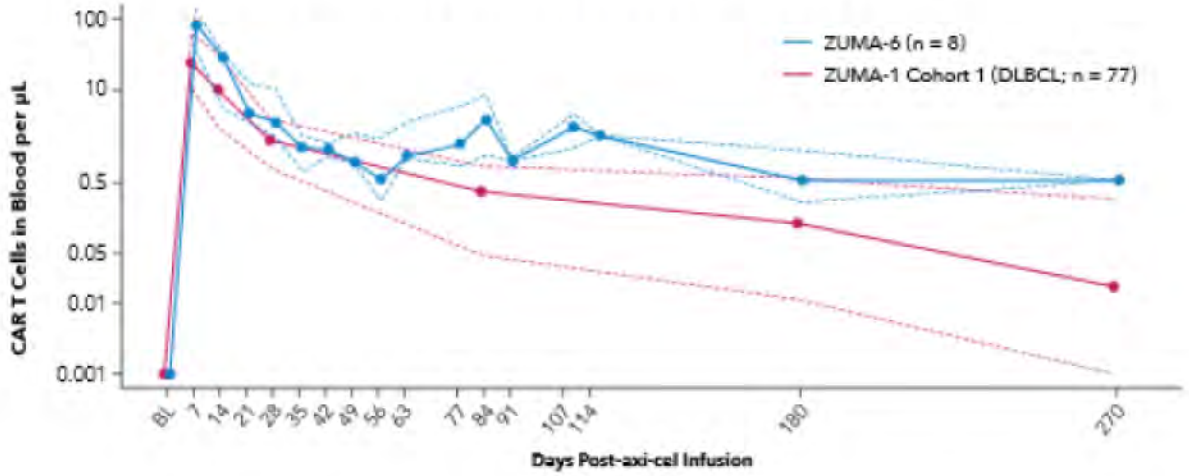
Abbreviations: ORR, objective response rate; NE, neurologic event; CRS, cytokine release syndrome; AUC, area under the curve; CAR, chimeric antigen receptor.
CAR AUC defined as cumulative levels of CAR + cells/μL of blood over the first 28 days after axicabtagene ciloleucel administration.
P values are calculated by Wilcoxon rank sum test.

Strategies that may enhance the engraftment of CAR T cells are currently being explored in the clinical setting. ZUMA-6 is a Phase 1/2 study examining axicabtagene ciloleucel in combination with atezolizumab (an anti PD-L1 mAb) in refractory DLBCL (NCT02926833). Programmed cell death protein 1 (PD-1) is an activation/exhaustion marker of cytolytic T cells and is upregulated on the surface of CAR T cells during in vitro exposure to CD19-expressing target cells {Bot 2015}. Further, in subjects treated with anti-CD19 CAR T cells, PD-1 is upregulated on CAR T cells after infusion {Perez 2015}. Based on the known biology of PD-1, upregulation could possibly lead to inhibition of cell division, cytolytic activity, and exhaustion of infused CAR T cells {Keir 2008}. Therefore, it was hypothesized that disruption of the PD-1/PD-L1 T-cell regulatory axis could enhance the cytolytic capacity of the infused CAR T cells and augment anti-CD19 CAR T-cell engraftment.

The Phase 1 portion of ZUMA-6 with axicabtagene ciloleucel in combination with atezolizumab has been completed with a manageable safety profile. There were no Grade 5 events, and the most common Grade 3/4 TEAEs were anemia 7 (78%), encephalopathy 5 (56%), neutropenia 4 (44%), hyponatremia 3 (33%), pyrexia 3 (33%), and thrombocytopenia 3 (33%). Overall, there was no evidence of worsening or recurrent AEs consistent with CRS, neurologic events (NE), or other CAR T-cell-related toxicities following atezolizumab administration {Locke 2017}.

After atezolizumab infusion, kinetics of CAR T cells suggest that atezolizumab may increase overall CAR T-cell AUC without increasing toxicity or changing the safety profile (Figure 3) {Locke 2017}. Atezolizumab administration on Day 1 at 1, 200 mg is currently being utilized in the Phase 2 cohort expansion portion of the study.

Figure 3. Post-infusion Kinetics of CAR T Cells in the Blood

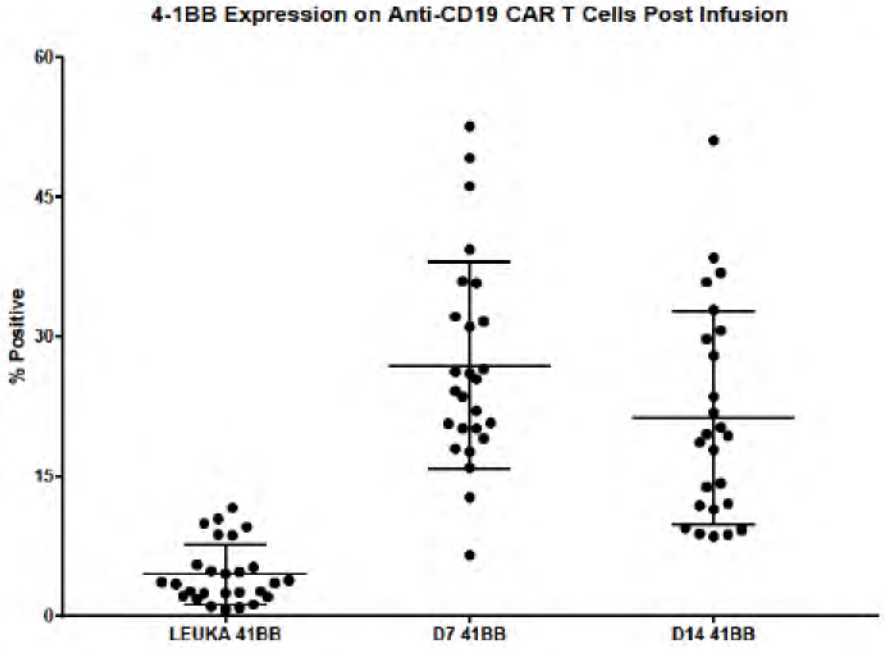


BL, baseline; CAR, chimeric antigen receptor; D, day; DLBCL, diffuse large B cell lymphoma; Mon, month; Wk, week.
Solid lines display median values. Dashed lines display the interquartile (Q1, Q3) range. Analysis was not available for 1 patient.

Similar to PD-1, 4-1BB expression is upregulated on anti-CD19 CAR T cells that are activated (Figure 4). Intracellular signaling downstream of 4-1BB engagement is known to enhance T--cell proliferation and effector function {Shuford 1997}, upregulate anti-apoptotic proteins {Hurtado 1997}, and promote survival and cell cycle progression {Lee 2003} and plays a critical role in the formation of immunological memory {Lee 2002}. Thus, agonism of 4-1BB on engineered anti-CD19 CAR T cells might enhance anti-tumor activity of axicabtagene ciloleucel via the following mechanisms: (1) increasing the viability of anti-CD19 CAR T cells through upregulation of anti-apoptotic proteins, (2) enhancing anti-CD19 CAR T-cell expansion and proliferation, and 3) contributing to the T-cell immune response. It is, therefore, possible that concomitant 4-1BB engagement could prevent primary and secondary resistance, support and sustain conversion of PR/SD to CR, and possibly prevent early relapse.

One possible concern is that enhanced CAR T-cell engraftment and activity may lead to increased toxicity. To mitigate this risk, a starting utomilumab total dose of 10 mg per dosing cycle has been chosen. This dose has been deemed to be safe as a both a single agent and in combination with rituximab. Further details on utomilumab dosing rationale are given in Section 3.2.3.

Figure 4. Upregulation of 4-1BB on CAR T Cells After Infusion



Abbreviations: CAR, chimeric antigen receptor; D, day; leuka, leukapheresis.
Upregulation of 4-1BB expression is seen on D7 after infusion relative to time of leukapheresis. 4-1BB upregulation is also seen on Day 14 after infusion, although declining in level relative to D7.

3. STUDY DESIGN

3.1. General Study Design

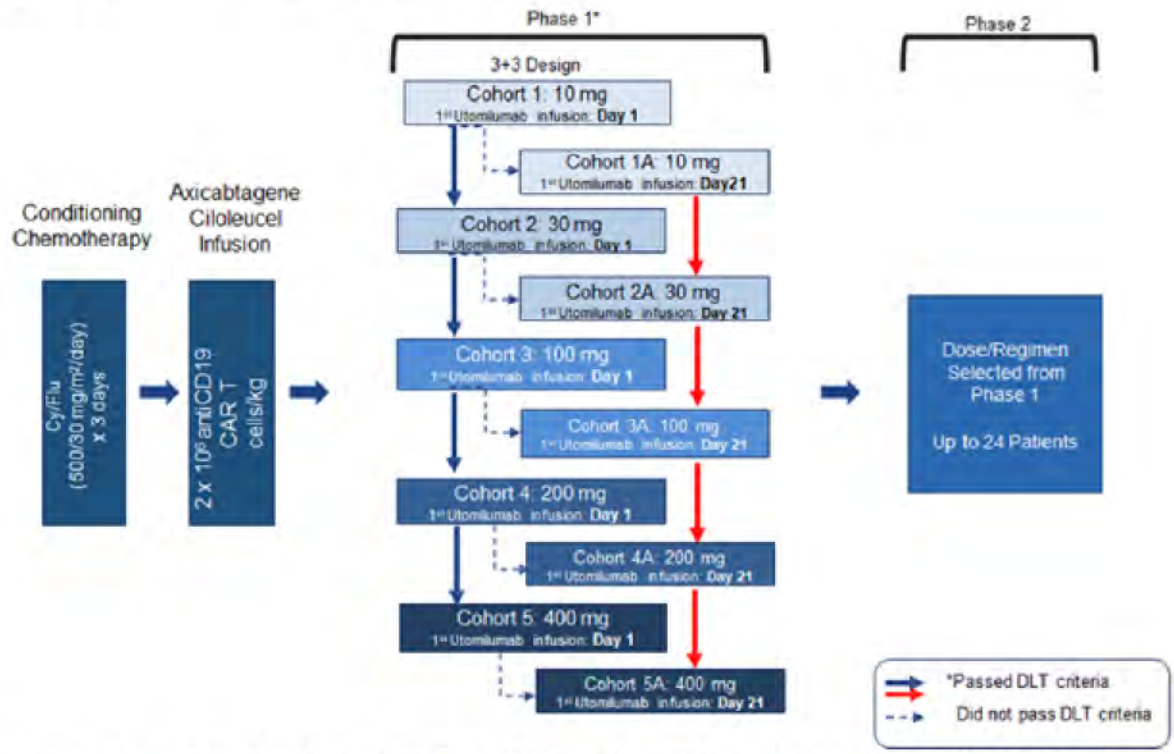
This is a Phase 1/2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with utomilumab administration in subjects with relapsed/refractory large B-cell lymphoma. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

During Phase 1, up to 36 subjects with relapsed/refractory large B-cell lymphoma will be enrolled in a 3+3 design in up to 6 of 10 cohorts to evaluate the safety of axicabtagene ciloleucel and utomilumab treatment regimens. Axicabtagene ciloleucel will be administered as a single dose, and utomilumab will be administered at escalating doses. Subjects will be enrolled and treated one at a time during the Phase 1 portion of the study. Subject treatment with axicabtagene ciloleucel will be staggered by at least 2 weeks.

Axicabtagene ciloleucel will be administered at a target dose of 2×10^6 anti-CD19 CAR T cells/kg on Day 0. Utomilumab will begin at a fixed dose of 10 mg on Day 1 in Cohort 1 (Figure 5). An internal safety review team (SRT), comprising the study sponsor and at least one Phase 1 investigator, will review safety data after all subjects in Cohort 1 complete the DLT window (28 days after the last subject in a cohort received the first utomilumab infusion). If Cohort 1 passes DLT criteria (see Section 9.10), then the study will proceed to Cohort 2. If Cohort 1 does not pass DLT criteria (see Section 9.10), then the study will proceed to Cohort 1A, which will explore the same fixed dose of utomilumab (10 mg) administered on Day 21. The SRT will make recommendations on further study conduct of Phase 1, including dose escalation to Cohort 2A (30 mg), or exploring additional dosing and/or timing of utomilumab administration as needed. The same rules will apply to Cohort 2, Cohort 3, Cohort 4, and Cohort 5. Refer to Figure 5 and Section 9.10.

At the conclusion of each SRT safety review meeting, the SRT will make recommendations on further study conducts outlined in Section 9.10.

Figure 5. Study Design Overview



* Utomilumab will be administered at total doses of 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg Q4W for 6 months unless there is disease progression.

Abbreviations: DLT, dose-limiting toxicity.

The Phase 1 Cohorts and utomilumab regimens administered are outlined in Table 2.

Table 2. Utomilumab Regimens

Dose Level*	Cohort	First Utomilumab Administration
10 mg	1	Day 1
	1A	Day 21
30 mg	2	Day 1
	2A	Day 21
100 mg	3	Day 1
	3A	Day 21
200 mg	4	Day 1
	4A	Day 21
400 mg	5	Day 1
	5A	Day 21

* Utomilumab total doses of 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg will be administered Q4W for 6 months or until progressive disease (PD), whichever comes first. The SRT will make recommendations on further study conduct of Phase 1.

In Phase 2, up to 24 subjects will be enrolled to receive axicabtagene ciloleucel and utomilumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the cohort or phase of the study, each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Bridging therapy, if applicable
- Conditioning chemotherapy
- Investigational product (IP) treatment (axicabtagene ciloleucel and utomilumab)
- Post-treatment assessment
- Long-term Follow-up (LTFU)

The SRT will additionally meet on at least 1 occasion during the Phase 2 portion of the study after 6 subjects have completed their 1-month disease assessment. The SRT will review safety and efficacy data and will be chartered to make trial conduct recommendations based on an analysis of benefit/risk ratio. Refer to Section 9.10.

For study requirement details assigned to each study period, refer to the schedule of assessments (SOAs) in Section 7.

A study schema is described in Figure 1.

3.2. Dosing Rationale

3.2.1. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlate with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in preclinical models, which demonstrate that the depth and duration of lymphodepletion correlates with anti-tumor activity of the adoptively transferred tumor-specific $CD8^+$ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine combination is a potent conditioning regimen. Cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) are both given for 3 consecutive days. This combination has been studied in subjects with B-cell malignancies and was tolerated by this population {O'Brien 2001}. Cyclophosphamide and fludarabine combination treatment was also used in the ZUMA-1 trial {Neelapu 2017b}.

3.2.2. Rationale for Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on the aggregate safety and efficacy data compiled from ZUMA-1 as outlined in the axicabtagene ciloleucel IB. Based on the favorable benefit/risk ratio seen in ZUMA-1, axicabtagene ciloleucel will be administered at a target dose of 2×10^6 anti-CD19 CAR T cells/kg, but may be dosed at a minimum of 1×10^6 anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, a maximum flat dose of axicabtagene ciloleucel at 2×10^8 anti-CD19 CAR T cells will be administered.

3.2.3. Rationale for Utomilumab Dose

Utomilumab (PF-05082566) showed a favorable toxicity profile in all clinical testing conducted thus far (Table 1; refer to Section 2.4.1). Single-agent utomilumab or in combination with rituximab was found to be safe with no DLTs up to 10mg/kg Q4W in study B1641001, a dose equivalent to 700mg in a 70-kg subject, and the MTD was estimated to be at least 10mg/kg Q4W. Treatment-related, treatment-emergent adverse events were mostly Grade 1 or -2 with only four Grade 3/4 AEs reported (colitis, diarrhea, fatigue, hyperbilirubinemia, and hyponatremia), Grade 3/4 colitis and diarrhea were observed in the same patient. No Grade 5 treatment-related AEs were observed.

Subsequently, preliminary population PK analysis was conducted using data from 68 subjects (n = 41 in Portion A and n = 27 from Portion B) from study B1641001, which indicated that the exposure at dose levels higher than 0.12 mg/kg (~8 mg in 70-kg subject) was above the assumed efficacious concentration (Ceff, 1730 ng/mL) with both once every 3 weeks (Q3W) and Q4W schedule. Briefly, efficacious concentration (Ceff) was estimated using the mean drug serum concentration of 11.5 nM (1730 ng/mL) from the biomarker, soluble CD137 (sCD137), and tumor growth inhibition (TGI) studies using a surrogate antibody (MaB9371), which has a similar affinity to mouse 4-1BB (KD = 12 nM) compared with that of PF-05082566 to human 4-1BB. For the biomarker sCD137, EC50 was estimated to be 11 nM (1650 ng/mL) using the indirect -response Emax model. For TGI, a complete response was achieved at 0.2 mg/kg (12 nM), which was consistent with the EC50 of 11nM estimated from the biomarker data. Hence, a mean drug serum concentration of 11.5 nM (1730 ng/mL) from the biomarker and TGI studies was used for human single-agent efficacious concentration/dose projection. Lastly, body weight accounted for only a small percentage (~<7%) of the inter-individual variability in serum PF-05082566 exposure, and also simulations indicated that PF-05082566 exposure was similar between body weight-based and fixed dosing regimens. CCI [redacted]

For this study, utomilumab was administered on Day 1 following axicabtagene ciloleucel administration in light of pre-existing and internal data, which shows upregulation of 4-1BB at 18 hours after CAR T-cell target engagement/activation (Figure 4 and data on file). In the event that any of the dose level/cohort with Day 1 utomilumab administration fails to pass the DLT criteria, Day 21 administration of utomilumab will be explored. Day 21 administration of utomilumab was chosen because by this time, the majority of subjects will have passed the window for acute axicabtagene ciloleucel-related toxicities and peak CAR T-cell expansion.

The starting dose of 10 mg (total dose) is 70-fold less than what has been shown to be safe as monotherapy or in combination with rituximab (10 mg/kg = 700 mg in a 70-kg subject). The 10-mg total dose was chosen to ensure safety of subjects on this study because the effect of utomilumab activity on axicabtagene ciloleucel is unknown.

At the dose escalation SRT review of the ZUMA-11, data for cohorts 1-3, no DLTs were observed. Worst grade CRS and NE were grade 2. No utomilumab dose delays due to toxicity were seen in all 3 cohorts. Grade 3/4 treatment related, treatment-emergent adverse events (TEAEs) were mostly cytopenias: anemia (44%), neutropenia (44%), lymphopenia (33%) and white blood cell count decreased (33%). There was no trend of increasing grade and/or rate of cytopenia with increasing dose of utomilumab. No treatment-related Gr 5 AEs were observed.

Further, a trend was observed between peak and cumulative levels ($AUC_{0\text{-}28d}$) of anti-CD19 CAR T-cells and utomilumab exposure. Median CAR T-cell peak levels were found to be 2.2 times higher (30 mg utomilumab cohort) and 4.7 times higher (100 mg utomilumab cohort) relative to ZUMA-1 Phase 2 Cohort 1.

In this same cohort of patients, peak levels of IL-2 and IFN-γ in serum increase in a dose-dependent manner with utomilumab exposure, potentially demonstrating enhanced T1 T cell activity. Myeloid associated cytokines and chemokines, previously associated with CRS and neurologic toxicity (Neelapu, NEJM 2017) showed no evidence of utomilumab dose-dependent increases commensurate with the lack of increased toxicity relative to ZUMA-1 Phase 2 Cohort 1.

The pharmacokinetic and pharmacodynamic results observed in the first three cohorts of ZUMA-11, combined with the clinical outcome results suggest that an increased dose of utolimumab could further enhance CAR T-cell proliferation and activity leading to an enhanced CR rate and durability of response with acceptable safety profile. It is acknowledged that these levels of utomilumab are substantially higher than the dose range determined for adequate exposure and target modulation in previous studies of utomilumab {Segal 2018}. However, the super-physiologic levels of T cells induced by CAR-T cell expansion in turn suggest higher levels of induced 4-1BB receptor concentration in setting of axi-cel compared to the physiologic levels seen in previous utomilumab studies. Therefore, the PK, PD data, and utomilumab dose levels determined from previous studies likely are not applicable in the setting of axi-cel and higher doses of utomilumab may be needed to achieve maximum 4-1BB receptor occupancy for maximum agonist activity.

3.3. Participating Sites

Approximately 8 centers located in North America will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

3.4. Number of Subjects

Participants in this trial will be referred to as "subjects." It is anticipated that approximately up to 60 subjects will be enrolled into this study as defined below:

- Phase 1: approximately 3 to 36 subjects
- Phase 2: approximately 24 subjects

3.5. Replacement of Subjects

Subjects will be replaced and continue to be enrolled until the specified number of subjects are attained in the DLT evaluable (Phase 1) and modified intent-to-treat (mITT) sets (Phase 2). See Section 10 for additional information. Subjects who receive between 1.0 and 2.4 x 10^6 anti-CD19 CAR T cells/kg or a flat dose of 2.0 x 10^8 anti-CD19 CAR T cells for subjects > 100 kg and who receive at least 1 dose of utomilumab will be considered evaluable in the efficacy analysis. Subjects who have not received an axicabtagene ciloleucel cell dose in this range or have not received at least 1 dose of utomilumab will be retained in the analyses of disposition and safety, where appropriate (Section 10.5).

3.6. Study Duration

3.6.1. 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 and survival, and if applicable, timing of transition to the separate LTFU study, KT-US-982-5968 (discussed in Section 3.6.3).

3.6.2. 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.

3.6.3. Long-term Follow-up

The subjects who received an infusion of 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 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 axicabtagene ciloleucel infusion (also refer to Section 7.11).

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 of 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.

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

101) Histologically proven large B-cell lymphoma, including the following types defined by {Swerdlow 2016}:

a) DLBCL not otherwise specified (activated B cell/germinal center B cell [ABC/GCB])

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

c) DLBCL arising from FL

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

e) DLBCL associated with chronic inflammation

f) Primary cutaneous DLBCL, leg type

g) Epstein-Barr virus (EBV) + DLBCL

102) Chemotherapy-refractory disease, defined as one or more of the following:

a) No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line systemic chemotherapy are excluded

i) Progressive disease (PD) as best response to first-line therapy

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

b) No response to second- or greater-lines of therapy

i) PD as best response to most recent therapy regimen

ii) SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy

OR

c) Refractory post-ASCT

i) Disease progression or relapsed $\leq$ 12 months after ASCT (must have biopsy proven recurrence in relapsed subjects)

ii) If salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

OR

d) Relapsed or refractory LBCL including DLBCL, TFL, and HGBCL after 2 lines of systemic therapy that is defined by and aligns with currently approved indication:

i) Relapsed disease after 2 lines of systemic therapy

OR

ii) Best response that is less than a CR to second line systemic therapy

103) At least 1 measurable lesion according to the 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.

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

a) Anti-CD20 mAb unless investigator determines that tumor is CD20 -negative, and

b) An anthracycline containing chemotherapy regimen

105) No radiographic evidence, suspicion, and/or history of central nervous system (CNS) involvement of lymphoma

106) 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.

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

108) Age 18 or older

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

110) Absolute neutrophil count (ANC) ≥ 1,000/μL

111) Platelet count ≥ 75,000/μL

112) Absolute lymphocyte count ≥ 100/μL

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

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

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

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

d) Cardiac ejection fraction ≥ 50% and no evidence of pericardial effusion within 180 days provided the subject did not receive an anthracycline-based treatment or experience a cardiac event or change in performance status

e) No clinically significant pleural effusion

f) Baseline oxygen saturation > 92% on room air

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

5.2. Exclusion Criteria

201) Histologically proven primary mediastinal B-cell lymphoma (PMBCL)

202) History of Richter's transformation of chronic lymphocytic leukemia (CLL)

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

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

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

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

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

208) Subjects with detectable cerebrospinal fluid (CSF) malignant cells, brain metastases, or a history of CNS lymphoma

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

210) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

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

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

213) Primary immunodeficiency

214) 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. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and subjects with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study

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

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

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

218) Live vaccine $\leq$ 6 weeks prior to planned start of conditioning chemotherapy

219) 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 post-menopausal for at least 2 years are not considered to be of childbearing potential.

220) Subjects of both genders who are not willing to practice birth control from the time of consent through 90 days after the last dose of utomilumab and at least 6 months after the completion of conditioning chemotherapy

221) History of malignancy other than non-melanoma skin cancer in situ (eg, cervix, bladder, breast) or low-grade (Gleason $\leq$ 6) prostate cancer or surveillance without any plans for treatment, unless disease-free for a least 3 years

222) ASCT within 6 weeks of planned enrollment

223) Prior organ transplantation including prior allogeneic stem cell transplant (SCT)

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

225) Use of any standard or experimental anti-cancer therapy within 2 weeks prior to enrollment, including cytoreductive therapy and radiotherapy, immunotherapy, or cytokine therapy (except for erythropoietin)

226) Prior treatment with PD-L1 inhibitor, PD-1 inhibitor, anti-CTLA4, anti-CD137 (4-1BB), anti-OX40 or other immune checkpoint blockade or activator therapy

227) Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IF] and interleukin-2 [IL-2]) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first utomilumab dose

228) History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening. History of radiation pneumonitis in the radiation field (fibrosis) is allowed.

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

6. PROTOCOL TREATMENT

6.1. Study Treatment

6.1.1. Leukapheresis

Leukapheresis refers to procedure for collecting PBMCs that are used to manufacture the subject-specific axicabtagene ciloleucel treatment.

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).

Leukapheresis may be repeated in case of manufacturing failure(s).

6.1.2. Bridging Therapy

At the discretion of the investigator, non-chemotherapy bridging therapy may be considered for subjects with high disease burden at screening or baseline assessments (eg, bulky disease or rapidly progressing disease). Bridging therapy regimens are outlined in Table 3. Bridging therapy will be supplied by the investigative site unless otherwise noted. Sites should refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management of bridging therapy.

Table 3. Bridging Therapy Regimens

Type	Therapy Regimens [a]	Timing and Washout Requirements
Corticosteroid	Dexamethasone at a dose of 20 mg to 40 mg or equivalent, either PO or IV daily for 1 to 4 days. Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines	May be administered after enrollment/leukapheresis and must be completed prior to the start of conditioning chemotherapy **Note:** PET-CT, chemistry panel, and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed
HDMP + Rituximab {Castro 2009}	1 gram/m^2 of high dose methylprednisolone (HDMP) for 3 days in combination with rituximab at 375 mg/m^2 weekly for 3 weeks	May be administered after enrollment/leukapheresis and completed at least 7 days prior to the start of conditioning chemotherapy **Note:** PET-CT, chemistry panel, and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed

Abbreviations: PET-CT, positron emission tomography–computed tomography; CBC, complete blood count.
[a] Bridging therapy regimen may be chosen at the discretion of the investigator.

6.1.3. Conditioning Chemotherapy

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

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

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

6.1.3.1. Cyclophosphamide

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

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

6.1.3.2. 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.

6.1.3.3. Mesna

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

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

6.1.4. Axicabtagene Ciloleucel

Axicabtagene ciloleucel is an IP for this study.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy and cream to yellow color. 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 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.

6.1.5. Utomilumab

6.1.5.1. Formulation, Packaging, and Handling

Utomilumab drug product will be supplied in clear glass vials at a 25 mg/mL (125 mg/vial) concentration as sterile solution for IV administration and labeled as open supplies. See the IPM for additional information.

6.1.5.2. Dosage, Administration, and Compliance

Utomilumab will be administered as an IV infusion once every four weeks (±2 days) starting on either Day 1 or Day 21 (depending on cohort). The starting dose of utomilumab will be 10 mg.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat allergic or anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat allergic and anaphylactic reactions. Subjects should be instructed to report any delayed reactions to the investigator immediately. From clinical trial experience, only occasional mild, infusion-related reactions have been observed, which did not require the usage of any concomitant medications or premedications.

The exact duration of infusion should be recorded in both sources document and case report forms (CRFs). The infusion rate should be reduced or interrupted in the case of symptoms of infusion reaction, and symptomatic treatment should be administered. The infusion may be

continued at one-half the previous rate upon improvement of symptoms. If symptoms persist or worsen, the infusion should be discontinued. The study drug dose escalation levels are shown in Table 2.

6.1.5.3. Dose Modification

No reduction or modification of utomilumab dose will be allowed within each cohort. Any toxicity associated or possibly associated with utomilumab treatment should be managed according to utomilumab IB. Additional laboratory tests or biopsies may be used to determine a possible immunogenic etiology.

Utomilumab may be withheld for up to 56 days. If utomilumab has to be withheld for > 56 days due to drug-related events without appropriate resolution, despite appropriate management, then utomilumab should be discontinued. However, if, in the investigator's judgment, the subject is likely to derive benefit from resuming utomilumab after a 56-day delay, utomilumab may be restarted only with the approval of the medical monitor.

Utomilumab dosing will be delayed for ongoing Grade 2 or higher CRS or Grade 2 or higher NEs. The delayed dose will be given upon resolution of CRS and neurologic events to Grade 1 or lower. If a dose is held > 10 days beyond the scheduled administration, it will not be given. Should an utomilumab dose be delayed ≤ 10 days, the remaining doses should be administered every 28 days (±2 days) from the onset date of first dose. Likewise, all protocol-required procedures should follow the same schedule, as outlined in the SOAs beginning on the onset date of the first dose.

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 therapies deemed necessary to provide adequate supportive care except those medications listed in Section 6.1.7.

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

For subjects who receive axicabtagene ciloleucel treatment:

- Concomitant therapies will be recorded from the date of the informed consent until 30 days after the final utomilumab infusion or for 12 weeks after completing treatment with axicabtagene ciloleucel (whichever is longer).
- After the post-treatment follow-up, targeted concomitant therapies will be recorded for either 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations.

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

For subjects who are not enrolled (eg, screen failure), concomitant therapies related to any serious adverse event(s) (SAEs) will be recorded.

Specific concomitant therapy collection requirements and instructions are included in the CRF 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 ($\geq$ 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 pre-medication to subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo non-contrast CT scans instead.

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

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

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

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

6.1.8. Subsequent Therapy

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

Subsequent therapy administered after investigational treatment that is necessary to treat a subject's LBCL, such as non-study specified chemotherapy, immunotherapy, targeted agents, stem cell transplant, or radiation therapy, will be recorded for all subjects dosed 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 investigational treatment infusion, any additional anti-cancer 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. Axicabtagene Ciloleucel Toxicity Management

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

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

6.1.10. Utomilumab Toxicity Management

Refer to the current utomilumab IB for details regarding toxicity management guidance.

7. STUDY PROCEDURES

Research staff should refer to SOA Table 5, Table 6, and Table 7 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. Refer to the CRF completion guidelines for data collection requirements and best practices for documentation of study procedures.

7.1. Informed Consent

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

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

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

7.2. Screening

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

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

After written informed consent has been obtained, Kite Pharma, Inc., will assign a screening number to the subject, as described in Section 4.

See Section 7.2.1 for the study procedures for subjects who rescreen into the study. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log, and the reasons for failing screening should also be recorded. The screening window is 28 days prior to enrollment.

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

7.2.1. Rescreening

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

7.3. Demographic Data

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

7.4. Medical and Treatment History

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

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

7.5. Physical Exam, Vital Signs, and Performance Status

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

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

For the first infusion of utomilumab, the subject's vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) should be determined within 60 minutes before the start of infusion, during the infusion (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the start of infusion. For subsequent utomilumab infusions, vital signs will be collected within 60 minutes before the start of infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the start of infusion.

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.

7.5.1. Cardiac Function

Each subject's cardiac function, as measured by left ventricular ejection fraction (LVEF), will be assessed during the screening period to confirm study eligibility. Evidence of no pericardial effusion will also be confirmed per study eligibility criteria. Both LVEF and presence of pericardial effusion will be assessed by echocardiogram (ECHO) prior to enrollment. An ECHO that was performed after the subject's last chemotherapy treatment may also be used to confirm eligibility, provided that it occurred ≤ 28 days prior to signing the consent.

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

7.6. Neurological Examination

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

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

Subjects will be specifically asked about changes in neurological status since the previous neurological examination, as noted in the SOA (see Table 5, Table 6, and Table 7).

7.7. Disease Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the Lugano Classification {Cheson 2014}; refer to Appendix 2. Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

7.7.1. Imaging

7.7.1.1. Imaging at Baseline

Each subject will undergo a screening brain magnetic resonance imaging (MRI) to rule out CNS metastasis during the screening period of the study.

To confirm eligibility and/or to establish a 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 at screening. PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility if within 28 days prior to enrollment, and no other anti-cancer treatment has been administered. If PET-CT is performed > 28 days prior to enrollment or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET-CT should be performed as close to enrollment as possible.

7.7.1.2. Post-treatment Response Assessment

The first planned post-treatment PET-CT tumor assessment will occur at Week 4.

PET-CTs will continue at time points outlined in the SOA through Month 24 or until disease progression, whichever comes first. If the subject's disease has not progressed by Month 24, disease assessments will continue to be performed per SOC. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if this requires an unscheduled visit.

7.7.1.3. Response Evaluation to Retreatment

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

7.7.2. Determination of Bone Marrow Involvement

A subject's bone marrow involvement should be confirmed by PET-CT or bone marrow biopsy and aspirate prior to the start of conditioning chemotherapy. Confirmation of marrow involvement can be determined upon initial diagnosis of disease or, if negative or unknown at initial diagnosis, at the time of relapse from first-line therapy.

If there is evidence of baseline bone marrow involvement and PET-CT is not available or if there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm complete response. The bone marrow aspirate and biopsy must show no evidence of disease by morphology, or, if indeterminate by morphology, it must be negative by immunohistochemistry (IHC). Refer to Appendix 2 for treatment response assessment requirements per the Lugano Classification {Cheson 2014}.

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

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

7.8.1. Leukapheresis

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

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

Before leukapheresis commences, the below criteria must be met:

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

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

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

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

Refer to the SOA Table 5 and Table 6 for a listing of study procedures to be completed on the leukapheresis collection day (prior to the start of leukapheresis). Local and central labs can be collected on the day prior to leukapheresis.

7.8.2. Conditioning Chemotherapy Period

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

Signs, symptoms, or abnormal laboratory results attributed to the malignancy (eg, "tumor fever," elevated C-reactive protein [CRP]) are considered to be diagnoses of exclusion and, thus, require a documented workup to demonstrate that all other possible diagnoses are ruled out.

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

Refer to Section 7.8.2.1 for requirements to work up potential infectious and/or inflammatory states.

7.8.2.1. Criteria Prior to Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the workup listed in Section 7.8.3.1.1. must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- White blood count (WBC) count or WBC differential concerning for infectious process between enrollment to start of conditioning 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 conditioning chemotherapy and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with conditioning chemotherapy.
- Complete history and physical exam, including head, eye, ear, nose, and throat (HEENT) and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of antimicrobials is allowed).
- Treatment course of any antimicrobials given for known or suspected antecedent infection should be complete as per infectious disease consult (if applicable) recommendation before stopping or switching to prophylactic antimicrobials.
- If a subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator in consultation with infectious disease service (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, polymerase chain reaction [PCR], stool studies, imaging studies) must be negative. If clinical suspicion is for an infection for which cultures are unlikely to be positive within 48 hours (eg, fungal infection), adequate time must be allowed for cultures to become positive.

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

7.8.2.2. Conditioning Chemotherapy Administration (Day –5 through Day –3 Prior to Axicabtagene Ciloleucel Infusion)

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

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

- IV hydration with a balanced crystalloid according to institutional guidelines prior to administration of cyclophosphamide on the day of infusion
- Cyclophosphamide 500 mg/m^2 IV over 60 minutes (± 15 minutes) followed by
- Fludarabine 30 mg/m^2 IV over 30 minutes (± 15 minutes) followed by
- Additional IV hydration with a balanced crystalloid according to institutional guidelines to be administered upon completion of infusion
- Mesna to be administered per institutional guidelines

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

Refer to the SOA Table 5 and Table 6 for a listing of study procedures to be completed during the conditioning chemotherapy period.

7.8.3. Investigational Product Treatment Period

7.8.3.1. Axicabtagene Ciloleucel Pretreatment Criteria

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the workup listed in Section 7.8.3.1.1. must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of axicabtagene ciloleucel infusion
- CRP > 100 mg/L anytime between enrollment to start of axicabtagene ciloleucel infusion
- WBC count or WBC differential concerning for infectious process between enrollment to start of axicabtagene ciloleucel infusion (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 axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam, including HEENT and cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems, must not reveal evidence of infection/inflammation.
- The subject must not have received systemic antimicrobials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel 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 axicabtagene ciloleucel.

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

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

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

- Call Kite medical monitor
- Infectious disease service consult (if available)
- CT imaging of the chest, abdomen, and pelvis with IV contrast. If there is a medical contraindication to contrast, then non-contrast CT is allowed.
- The following must be performed (prior to the initiation of antimicrobials if clinically feasible):
  - Blood cultures (aerobic and anaerobic x2 bottles each) and urinary analysis 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 (NPT) swab or equivalent assay for viral infection, such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus
  - Collection of fungal cultures and markers as appropriate (eg, galactomannan, Fungitell®)
  - Collection of appropriate serum viral studies (eg, cytomegalovirus [CMV])
- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.
- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

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

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

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

7.8.3.2. Axicabtagene Ciloleucel Premedication Dosing

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

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

7.8.3.3. Axicabtagene Ciloleucel Administration Day 0

All subjects will receive axicabtagene ciloleucel infusion at a healthcare facility, followed by daily monitoring at a healthcare facility for at least 7 days to monitor for signs and symptoms of CRS and NEs. Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and NEs 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 non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency), even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing axicabtagene ciloleucel-related fever, hypotension, hypoxia, or ongoing NEs > 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, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.

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

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administering of axicabtagene ciloleucel are outlined in the IPM. Vital signs should be measured during and after axicabtagene ciloleucel treatment (see Section 7.5). The IPM must be reviewed prior to administration of axicabtagene ciloleucel.

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

7.8.3.4. Utomilumab Administration

Utomilumab treatment consists of an IV infusion given every 4 weeks for 6 months or until disease progression, whichever comes first. In the Phase 1 portion of the study, the doses of utomilumab administered will be 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg beginning at either Day 1 or Day 21 after axicabtagene ciloleucel infusion. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 5 and outlined in Section 9.10.

Subjects will remain in clinic for post-utomilumab observation for at least 2 hours after the end of the first infusion of utomilumab and for at least 1 hour after the end of subsequent infusions.

For more detailed information regarding administration, refer to the IPM and IB.

7.8.3.5. Axicabtagene Ciloleucel Retreatment

Subjects who achieve a PR or CR and subsequently experience disease progression may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel while enrolled in this study. The second course of treatment must be given within 24 months of the initial axicabtagene ciloleucel infusion.

In either case, the following criteria must be met in order to be considered for a repeat course of therapy:

- Subject had a PR or CR at the first disease assessment at Week 4 but subsequently experienced progression of disease at a later time.
- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to retreatment.
- Subject continues to meet the original study eligibility criteria with the exception of prior axicabtagene ciloleucel use in this study; screening assessments and procedures should be repeated if clinically indicated (eg, MRI, ECHO)
- Subject has not received subsequent therapy for the treatment of lymphoma.
- Subject did not experience a life-threatening (Common Terminology Criteria For Adverse Events [CTCAE] Grade ≥ 4) toxicity related to axicabtagene ciloleucel during the original course of treatment.

- Toxicities related to conditioning chemotherapy (cyclophosphamide and fludarabine), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment.
- Subject does not have known axicabtagene ciloleucel neutralizing antibodies (exception: if a non-neutralizing axicabtagene ciloleucel antibody develops, subject may be retreated if the original study eligibility criteria are met).
- Subject meets axicabtagene ciloleucel pretreatment criteria.

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

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

A maximum of 1 retreatment course may occur per subject.

Allowance for retreatment is based on clinical experience in ZUMA-1, where a total of 10 subjects were retreated with axicabtagene ciloleucel (1 subject in Phase 1 and 9 subjects in Phase 2). Overall, 6 of 10 retreated subjects had a PR or CR to the retreatment. The subject in Phase 1 achieved a PR at Month 1 after retreatment. Among the 9 subjects retreated in Phase 2, five subjects responded (2 CR and 3 PR) at Month 1. Analysis of duration of retreatment response (DORR) among the retreated subjects in Phase 2 showed a median DORR of 3.5 months as of the data cutoff date. Results were identical in a sensitivity analysis that excluded responses in 4 subjects who underwent ASCT following retreatment.

After a subject is deemed eligible for retreatment and the means by which the second dose of axicabtagene ciloleucel has been confirmed (which will include determining whether a second leukapheresis is required), the subject will follow the same study procedure requirements that were followed during his or her initial course of treatment with the exception of utomilumab infusions.

7.9. Laboratory

7.9.1. Local Lab Analysis

Assessments listed in Table 4 will be performed at the local laboratory at the time points indicated in the SOA. Additional samples (eg, blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Table 4. Local Laboratory Parameters

Serum Chemistries	Hematology	Other
Albumin	CBC with differential[b]	CRP
ALT/GPT		Ferritin
ALP		Pregnancy test[c]
AST/GOP		
Bicarbonate total		
Bilirubin direct		
Bilirubin total		
BUN or urea[a]		
Calcium total		
Chloride		
Creatinine		
Creatinine clearance		
Glucose		
Inorganic Phosphorus		
LDH		
Magnesium total		
Potassium		
Sodium		
Uric acid[b]		

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; GOP, serum glutamic-oxaloacetic transaminase; GPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase.

a If BUN test cannot be analyzed by the local lab, urea should be analyzed.
b Per institutional guidelines.
c Women of childbearing potential only.

7.9.2. Central Laboratory Analyses

Biomarker analysis will be performed on blood, CSF, and tumor samples to evaluate PK and pharmacodynamic markers for axicabtagene ciloleucel in conjunction with utomilumab. Prognostic markers for aggressive NHL and related to the tumor immune environment may also be evaluated.

Clinical biospecimens (eg, tumor tissue, bone marrow, complete blood, CSF, or other bodily fluids) will be sent from clinical study centers to the central laboratory for sample processing, accessioning, and distribution to specialty laboratories or Kite. Samples will be obtained at the times indicated in the SOA. Additional samples (eg, complete blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Apheresis and product retains are provided to the central lab or are stored at a Kite sponsored central laboratory. Complete instructions regarding sample submission to central laboratories are provided in the Central Laboratory Manual.

- Samples to be collected by study sites:
  - Tumor tissue
    - Archival tumor tissue or on-study tumor biopsy at baseline if archival tissue is not available

    CCI [redacted]

    CCI [redacted]
  - Blood for a central CBC with differential, PK (levels of anti-CD19 CAR T cells), replication-competent retrovirus (RCR) testing, and assessment of B-cell aplasia and immune reconstitution
  - Serum for pharmacodynamics (cytokine levels)
  - CSF for determination of PK, pharmacodynamics, presence of CAR T cells and other immune cell subsets

CCI [redacted] Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the central laboratory. The investigator should provide the sponsor with the study and subject ID number so that the sample can be located and destroyed. For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor, and any data that may be generated from these samples will be entered in the study database. Complete details concerning these analyses will be provided in separate documents regarding bioanalytical analyses.

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

CCI [redacted]

CCI

CCI

7.9.2.2. Pharmacokinetics and Pharmacodynamics for Axicabtagene Ciloleucel

PK and pharmacodynamics analysis will be performed on blood (levels of anti-CD19 CAR T cells) or serum (cytokines) at the intervals outlined in the SOA to evaluate predictive markers for the efficacy and safety of axicabtagene ciloleucel. The following cytokines and chemokines may be included in the panel: homeostatic, pro-inflammatory, and immune modulating cytokines IL-2, IL-6, IL-10, IL-12p40/p70, IL-15, IL-17a, TNF-α, IFN-γ, and granulocyte macrophage-colony stimulating factor (GM-CSF); acute phase reactants, such as CRP, chemokines IL-8, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and IP-10; and HLH related markers ferritin and IL-2Rα.

CSF and additional samples (eg, pleural fluid) will be collected at baseline and at post-infusion time points outlined in the SOA to enable evaluation of inflammatory cytokines and chemokine levels for determination of PK, pharmacodynamics, and presence of CAR T cells and other immune cell subsets. CSF draws and additional subject samples (eg, pleural fluid) will be obtained from subjects who develop Grade $\geq$ 2 NEs for evaluation of inflammatory cytokine and chemokine levels and presence of anti-CD19 CAR T cells. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.

7.9.2.3. Pharmacokinetic and Anti-drug Antibody Assessments for Utomilumab

Instruction manuals and supply kits will be provided by the central laboratory for all samples. The following samples will be sent to the central laboratory and then to a sponsor-designated bioanalytical laboratory or to the sponsor for analysis. Details regarding the collection, processing, storage, and shipping of blood samples will be provided in the Central Laboratory Manual.

7.9.2.3.1. Sample Collections for Subjects with Utomilumab Administered Started on Day 1

- Serum samples will be assayed for the presence of anti-drug antibodies (ADAs) to utomilumab with the use of validated immunoassays. ADA samples are to be collected at the following time points (in relation to utomilumab infusion):
  - — Infusion 1 and 2: prior to infusion
  - — At the post-treatment follow-up visit

- Serum samples will be assayed for utomilumab concentrations with the use of a validated analytical method. PK samples are to be collected at the following time points (in relation to utomilumab infusion):

  — Infusion 1: prior to infusion; end of infusion; and on Days 3, 7, 14 (Week 2), and 21 (Week 3) following utomilumab infusion

  — Infusions 2 and 4: prior to infusion; end of infusion; and 2 days following utomilumab infusion 2

  — At the post-treatment follow-up visit

7.9.2.3.2. Sample Collections for Subjects with Utomilumab Administered Starting on Day 21

- ADA samples are to be collected at the following time points (in relation to utomilumab infusion):

  — Infusion 1 and 2: prior to infusion

  — At the post-treatment follow-up visit

- PK samples are to be collected at the following time points (in relation to utomilumab infusion):

  — Infusion 1: prior to infusion, end of infusion, and 2 and 8 (Week 4) days following the utomilumab infusion

  — Infusions 2 and 4: prior to infusion; end of infusion; and 2 days following utomilumab infusion 2

  — At the post-treatment follow-up visit

7.9.2.3.3. Sample Collections for Subjects in Phase 2

- Serum samples will be assayed for the presence of ADAs to utomilumab with the use of validated immunoassays. ADA samples are to be collected at the following time points (in relation to utomilumab infusion):

  — Infusion 1 and 2: prior to infusion

  — At the post-treatment follow-up visit

- Serum samples will be assayed for utomilumab concentrations with the use of a validated analytical method. PK samples are to be collected at the following time points (in relation to utomilumab infusion):

  — Infusion 1, 2, and 4: prior to and following the end of infusion

7.9.2.4. Product Characteristics

In addition, baseline leukapheresis and final axicabtagene ciloleucel samples will be banked and may be analyzed by immunophenotyping, quantitative polymerase chain reaction (qPCR), and/or gene expression profiling. CCI [redacted]

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

7.9.2.5. RCR Testing

Axicabtagene ciloleucel comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. RCR testing will occur at the following time points: baseline, Week 12, Week 20/23 (depending on cohort), and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up to 15 years or as clinically indicated. Additional information is provided in the axicabtagene ciloleucel IB.

7.10. Post-treatment Assessment Period

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

If a subject does not respond to treatment at any time during the study, then the subject will continue to undergo follow-up procedures and then be followed for survival and disease outcomes in the LTFU portion of the study.

Refer to the SOAs for a listing of study procedures and disease assessments to be completed during the post-treatment follow-up period.

7.11. Long-term Follow-up Period

All enrolled subjects will be followed in the LTFU period for safety analysis and survival and disease status, if applicable. Subjects will begin the LTFU period after completion of the post-treatment follow-up visit (whether they have responded to treatment or went straight to the post-treatment follow-up visit due to disease progression). 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 signed informed consent. Subjects who did not respond to treatment will continue to be followed for disease assessments (if progression was not documented), subsequent anti-cancer therapy, and survival.

Subjects may also be contacted by telephone to confirm survival status and subsequent anti-cancer therapy use. If the subject fails to return to the clinic for a scheduled protocol-specific visit, sites will need to make 2 attempts, using both the telephone and either mail or email to

contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, then the subject will be considered lost to follow-up, and no additional contact will be required.

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

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

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per protocol
- AE/SAEs per Section 9

Table 5. Schedule of Assessments Cohort 1, 2, 3, 4, 5 and Phase 2 (as applicable) Utomilumab Administration Starting on Day 1

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy			IP Administration Period										Post-treatment Follow-up
Day	Within 28 days of enrollment		-5	-4	-3	0	1	2-7	Week 2 (14± 2 days)	Week 3 (21± 2 days)	Week 4 (28± 3 days)	Week 8 (± 1 week)	Week 12 (± 1 week)	Week 16 (± 1 week)	Week 20 (± 1 week)	30 days (± 1 week) following last utomilumab infusion
Utomilumab Infusion #							#1				#2	#3	#4	#5	#6	
Medical History	X															
ECOG Performance Status	X															
12-lead ECG	X															
ECHO	X															
Brain MRI	X															
Neurological Assessment	X					X	QOD[1]									
PET-CT/ Disease Assessment[2]	X										X		X			X
Archival/Fresh Tumor[3]		X						D5								
Post-Progression Biopsy[4]																X
Physical Exam	X		X			X	X	X	X		X	X	X	X	X	X
Vital Signs (BP, HR, O_2 saturation, RR, Temperature)[5]	X	X	X	X	X	X	X[15]	X	X	X	X[15]	X[15]	X[15]	X[15]	X[15]	X
Weight (plus Height at screening)	X	X														
Pregnancy Test[6] (serum or urine)	X												X			X
Lumbar Puncture[7]		X						D5			X					
Blood Draw for Chemistry Panel	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy			IP Administration Period										Post-treatment Follow-up
Day	Within 28 days of enrollment		-5	-4	-3	0	1	2-7	Week 2 (14± 2 days)	Week 3 (21± 2 days)	Week 4 (28± 3 days)	Week 8 (± 1 week)	Week 12 (± 1 week)	Week 16 (± 1 week)	Week 20 (± 1 week)	30 days (± 1 week) following last utomilumab infusion
Utomilumab Infusion #							#1				#2	#3	#4	#5	#6	
Blood Draw for CBC w/Differential	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Blood Draw for CRP		X														
Blood Draw for Cytokines[8, 9]		X				X	X	D3, D7, D14		X	X[9]	X[9]	X[9]			
Central CBC w/Differential and PBMC[8, 10]		X				X	X	D3, D7, D10, D14		X	X[10]	X[10]	X	X	X	X
Blood Draw for Utomilumab PK[11]							X	D3, D7	X	X	X		X			X
Blood Draw for Utomilumab ADA[12]							X				X					X
Leukapheresis		X														
Cyclophosphamide/Fludarabine			X	X	X											
Axicabtagene Ciloleucel Infusion IV						X										
Utomilumab Infusion IV[13]							D1				D29	D57	D85	D113	D141	
Adverse Events/ Concomitant Medication[14]	X															

Abbreviations: CBC, complete blood count; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography-computed tomography; SAE, serious adverse event; IP, investigational product; D, day; IV, intravenous; ADA, anti-drug antibody; CRP, C-reactive protein; PK, pharmacokinetics; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; MRI, magnetic resonance imaging; BP, blood pressure; HR, heart rate; RR, respiration rate; QOD, <define acronym>.

1 Assessments on Day 1, every other day until Day 7, and as clinically indicated thereafter.

2 PET-CT (Neck-Chest-Abdomen-Pelvis)/Disease Assessment: PET-CT performed following the subject's last line of therapy and prior to signing the informed consent may be used for confirmation of eligibility if within 28 days prior to enrollment and no other anti-cancer treatment has been administered. If PET-CT is performed > 28 days prior to enrollment or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET-CT will also be performed at Week 4, Week 12, and at the post-treatment follow-up visit.

3 Sites are strongly encouraged to submit archival/fresh tumor sample: Either formalin-fixed paraffin embedded (FFPE) tumor block or up to 20 unstained slides. Archived and fresh tumor samples will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. CCI [redacted]

4 CCI [redacted]

5 It is recommended that vital signs are monitored during and after axicabtagene ciloleucel treatment and as clinically indicated.

6 Pregnancy test to be conducted at screening, Week 12, and the post-treatment follow-up visit.

7 Lumbar Puncture: CSF sample collection will be performed in subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion. CCI [redacted]

8 If a subject is subsequently re-admitted to the hospital following IP administration period with any axicabtagene ciloleucel related adverse events, blood samples for central CBC w/differential, PBMC, and cytokines will be collected on day of hospital re-admission and then weekly through and including the day of discharge. Blood samples for PBMC and cytokines should also be collected at the time of disease progression prior to starting any subsequent anti-cancer therapy.

9 Blood draw for Cytokines: enrollment, prior to axicabtagene ciloleucel infusion on Day 0, and on Days 3, 7, 14 (Week 2), 21 (Week 3), and Month 3 (Week 12). Cytokines also to be collected prior to the first 3 utomilumab infusions (on Day 1, Day 29, and Day 57). Post utomilumab infusion cytokine collection to occur 2 days after first 3 infusions of utomilumab (Day 3, Day 31, and Day 59).

10 Blood draw for Central CBC w/Differential and PBMC: enrollment; prior to axicabtagene ciloleucel infusion on Day 0; and on Days 3, 7, 10, 14 (Week 2), and 21 (Week 3). PBMC to be collected prior to each utomilumab infusion starting on Day 1 and every 4 weeks. Post utomilumab infusion PMBC collection to occur 2 days after first 3 infusions of utomilumab (Day 3, Day 31, and Day 59).

11 Blood draw for utomilumab Pharmacokinetics: In Phase 1, blood samples will be collected pre-dose and end of utomilumab infusion 1 on Day 1 as well as on Days 3, 7, 14, (Week 2), and 21 (Week 3); samples to be collected at pre-dose and end of utomilumab infusion 2 (Week 4) and 4 (Week 12) as well as 2 days after utomilumab infusion 2 (Day 31); samples to be collected at the post-treatment follow-up visit. In Phase 2, blood samples will be collected pre-dose and end of utomilumab infusion 1 (Day 1), 2 (Week 4), and 4 (Week 12).

12 Blood draw for utomilumab Immunogenicity (ADA): Blood for immunogenicity testing will be collected prior to utomilumab infusion 1 (Day 1), 2 (Week 4), and at the post-treatment follow-up visit.

13 Utomilumab dosing starts on study Day 1 and continues every 4 weeks (± 2 days) for 6 months (6 infusions) or until PD (whichever is sooner).

14 SAE reporting begins after signing of the informed consent. AE/concomitant medication reporting begins after enrollment.

15 For the first infusion of utomilumab, the subject's vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) should be determined within 60 minutes before the start of the infusion, during the infusion (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the start of infusion. For subsequent utomilumab infusions, vital signs will be collected within 60 minutes before the start of infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the start of infusion.

Table 6. Schedule of Assessments Cohort 1A, 2A, 3A, 4A, 5A and Phase 2 (as applicable) Utomilumab Administration Starting on Day 21

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy			IP Administration Period											Post-treatment Follow-up
Day	Within 28 days of enrollment		-5	-4	-3	0	1-7	Week 2 (14±2 days)	Week 3 (21± 2 days)	Week 4 (28± 3 days)	Week 7 (±1 week)	Week 11 (±1 week)	Week 12[18] (±1 week)	Week 15 (±1 week)	Week 19 (±1 week)	Week 23 (±1 week)	30 days (± 1 week) following last utomilumab infusion
Utomilumab Infusion #									#1		#2	#3		#4	#5	#6	
Medical History	X																
ECOG Performance Status	X																
12-lead ECG	X																
ECHO	X																
Brain MRI	X																
Neurological Assessment	X					X	QOD[1]										
PET-CT/Disease Assessment[2]	X									X			X				X
Archival/Fresh Tumor[3]		X					D5										
Post-Progression Biopsy[4]																	X
Physical Exam	X		X			X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, O_2 saturation, RR, Temperature)[5]	X	X	X	X	X	X	X	X	X[16]	X	X[16]	X[16]	X	X[16]	X[16]	X[16]	X
Weight (plus Height at screening)	X	X															
Pregnancy Test[6] (serum or urine)	X												X				X
Lumbar Puncture[7]		X					D5			X							
Blood Draw for Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Draw for CBC w/Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures	Screening	Enrollment/ Leukapheresis	Conditioning Chemotherapy			IP Administration Period											Post-treatment Follow-up
Day	Within 28 days of enrollment		-5	-4	-3	0	1-7	Week 2 (14±2 days)	Week 3 (21± 2 days)	Week 4 (28± 3 days)	Week 7 (±1 week)	Week 11 (±1 week)	Week 12[16] (±1 week)	Week 15 (±1 week)	Week 19 (±1 week)	Week 23 (±1 week)	30 days (± 1 week) following last utomilumab infusion
Utomilumab Infusion #									#1		#2	#3		#4	#5	#6	
Blood Draw for CRP		X															
Blood Draw for Cytokines[8, 9]		X				X	D1, D3, D7, D14		X[9]	X	X[9]	X[9]	X[9]				
Central CBC w/Differential and PBMC[8, 10]		X				X	D1, D3, D7, D10, D14		X[10]	X	X[10]	X[10]	X	X	X	X	X
Blood Draw for Utomilumab PK[11]									X[11]	X	X			X			X
Blood Draw for Utomilumab ADA[12]									X		X						X
Leukapheresis		X															
Cyclophosphamide/Fludarabine			X	X	X												
Axicabtagene Ciloleucel Infusion IV						X											
Utomilumab Infusion IV[13]									D21		D49	D77		D105	D133	D161	
Adverse Events/ Concomitant Medication[15]	X																

Abbreviations: CBC, complete blood count; PBMC, peripheral blood mononuclear cell; PET-CT, positron emission tomography computed tomography; SAE, serious adverse event; IP, investigational product; D, day; IV, intravenous; ADA, anti-drug antibody; CRP, C-reactive protein; PK, pharmacokinetics; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; MRI, magnetic resonance imaging; BP, blood pressure; HR, heart rate; RR, respiration rate; QOD, <define acronym>.

1 Assessments on Day 1, every other day until Day 7, and as clinically indicated thereafter.

2 PET-CT (Neck-Chest-Abdomen-Pelvis)/Disease Assessment: PET-CT performed following the subject's last line of therapy and prior to signing the informed consent may be used for confirmation of eligibility if within 28 days prior to enrollment and no other anti-cancer treatment has been administered. If PET-CT is performed > 28 days prior to enrollment or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the PET-CT scan must be repeated to establish a new baseline. PET-CT will also be performed at Week 4, Week 12, and at the post-treatment follow-up visit.

3 Sites are strongly encouraged to submit archival/fresh tumor sample: Either formalin-fixed paraffin embedded (FFPE) tumor block or up to 20 unstained slides. Archived and fresh tumor samples will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. CCI [redacted].

[redacted]

5 It is recommended that vital signs are monitored during and after axicabtagene ciloleucel treatment and as clinically indicated.

6 Pregnancy test to be conducted at screening, Week 12, and the post-treatment follow-up visit.

7 Lumbar Puncture: CSF sample collection will be performed in subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion. CCI [redacted]

8 If a subject is subsequently re-admitted to the hospital following IP administration period with any axicabtagene ciloleucel related adverse events, blood samples for central CBC w/differential, PBMC, and cytokines will be collected on day of hospital re-admission and then weekly through and including the day of discharge. Blood samples for PBMC and cytokines should also be collected at the time of disease progression prior to starting any subsequent anti-cancer therapy.

9 Blood draw for Cytokines: enrollment; prior to axicabtagene ciloleucel infusion on Day 0; and on Days 1, 3, 7, 14 (Week 2), 28 (Week 4), and Month 3 (Week 12). Cytokines to be collected prior to the first 3 utomilumab infusions (on Day 21, Day 49, and Day 77). Post-utomilumab infusion cytokine collection to occur 2 days after the first 3 infusions of utomilumab (Day 23, Day 51, and Day 79).

10 Blood draw for Central CBC w/Differential and PBMC: enrollment; prior to axicabtagene ciloleucel infusion on Day 0; and on Days 1, 3, 7, 10, 14 (Week 2), and 28 (Week 4). PBMC to be collected prior to each utomilumab infusion starting on Day 21 and every 4 weeks. Post-utomilumab infusion PMBC collection to occur 2 days after first 3 doses of utomilumab (Day 23, Day 51, and Day 79).

11 Blood draw for utomilumab Pharmacokinetics: In Phase 1, blood samples will be collected pre-dose and end of utomilumab infusion 1 on Day 21, as well as 2 days and 8 days (Week 4) following the first infusion; samples to be collected at pre-dose and end of utomilumab infusion 2 (Week 7) and 4 (Week 15) as well as 2 days after utomilumab infusion 2 (Day 51); samples to be collected at the post-treatment follow-up visit. In Phase 2, blood samples will be collected pre-dose and end of utomilumab infusion 1 (Day 21), 2 (Week 7), and 4 (Week 15).

12 Blood draw for utomilumab Immunogenicity (ADA): Blood for immunogenicity testing will be collected prior to infusion 1 (Week 3), 2 (Week 7), and at the post-treatment follow-up visit.

13 Utomilumab dosing starts on study Day 21 and continues every 4 weeks (±2 days) for 6 months (6 infusions) or until PD (whichever is sooner).

14 Week 12 visit can be conducted at the same time as Week 11, if within window of assessment.

15 SAE reporting begins after signing of the informed consent. AE/concomitant medication reporting begins after enrollment.

16 For the first infusion of utomilumab, the subject's vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) should be determined within 60 minutes before the start of the infusion, during the infusion (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the start of infusion. For subsequent utomilumab infusions, vital signs will be collected within 60 minutes before the start of infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (±10 minutes) after the start of infusion.

Table 7. Long-term Follow-up Assessments

Procedure	Long-term Follow-up Period[7,8]											
Visit Frequency	Month 9 (± 2 weeks)	Month 12 (± 2 weeks)	Month 15 (± 2 weeks)	Month 18 (± 2 weeks)	Month 24 (± 1 month)	Month 30 (± 1 month)	Month 36 (± 1 month)	Month 42 (± 1 month)	Month 48 (± 1 month)	Month 54 (± 1 month)	Month 60 (± 1 month)	Month 72 and Annually Thereafter for 15 Years (± 1 month)
Physical Exam[1]	X	X	X	X	X							
PET-CT/Disease Assessment[2]	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
CCI												
Survival Status	X	X	X	X	X	X	X	X	X	X	X	X
Blood Draw for Chemistry Panel	X	X	X	X	X							
Blood Draw for CBC w/Differential	X	X	X	X	X							
Central CBC w/Differential and PBMC	X	X	X	X	X		X		X		X	X
Targeted AE/SAEs[4]	X	X	X	X	X	X	X	X	X	X	X	X
Targeted Concomitant Medication[5]	X	X	X	X	X							
Subsequent Therapy for NHL[6]	X	X	X	X	X	X	X	X	X	X	X	X

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

1 Physical exams will continue through Month 24.

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

[redacted]

4 Targeted AEs/SAEs (see Section 9.2) will be collected for 24 months or until disease progression (whichever occurs first).

5 Targeted concomitant medications (see Section 6.1.6) will be collected for 24 months or until disease progression (whichever occurs first).

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

7 In the event of PD, subject will begin the LTFU period after completion of the post-treatment follow-up visit and be assessed for survival and subsequent therapy.

8 In the event this study is terminated prior to the completion of the 15-year follow up for all subjects, 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. The subject's final on-study visit for this study may be combined with the first visit on the LTFU study. The timing of the final on-study visit/first LTFU study visit will depend on the timing of the collection of all the subject's data that are required for the planned analysis for this study.

8. SUBJECT WITHDRAWAL

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

Subjects can decline to continue to receive study-required treatment and/or other protocol required procedures at any time during the study while continuing to participate in the study. This is referred to as partial withdrawal of consent. Refer to Section 8.3 for instructions on follow-up and data to be collected.

Withdrawal of full consent from a study means that the subject does not wish to receive further protocol-required therapy, undergo procedures, and continue participating in study follow-up. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study (refer to Section 8.3).

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

8.1. Reasons for Removal from Treatment

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

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

8.2. Reasons for Removal from Study

Reasons for removing a subject from the study are as follows:

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

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

If partial withdrawal of consent occurs (defined in Section 8), the investigator must discuss with the subject the appropriate process for discontinuation from IP 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 (Table 5, Table 6, and Table 7). 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.

If withdrawal of full consent occurs (defined in Section 8), the investigator is to discuss with the subject the appropriate procedures for withdrawal from the study. If a subject withdraws full consent, subject data collected up to withdrawal of consent will be retained and included in the analysis of the study, and where permitted by local regulations, publicly available data (eg, death records).

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

9. SAFETY REPORTING

9.1. Adverse Events

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

An AE does not include the following:

- A pre-existing condition that has not worsened during the study or involves an intervention (such as elective cosmetic surgery or a medical procedure) while on study
- Interventions for pretreatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation
- Hospitalization for study treatment infusions or study-mandated procedures or hospitalization as a precautionary measure per institutional policy
- The term "disease progression," as assessed by measurement of malignant lesions on radiographs or other methods is not considered to be an AE. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, B-cell lymphoma).

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

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

9.2. Reporting of AEs

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject that occur after enrollment through 30 days after completing the final dose of utomilumab or 12 weeks after the axicabtagene ciloleucel infusion, whichever is longer. For subjects who are enrolled, but do not receive axicabtagene ciloleucel, the AE reporting period ends 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy). After that, only targeted AEs will be reported through 24 months after

axicabtagene ciloleucel infusion or disease progression, whichever occurs first, and will be recorded in the eCRF

Targeted AEs include neurological events, hematological events, infections, GVHD, autoimmune disorders, and secondary malignancies. Secondary malignancies are defined as the development of any new malignancies, with the exception of a relapse of the primary malignancy, occurring after the administration of study treatment.

All AEs deemed related to axicabtagene ciloleucel infusion or utomilumab should be recorded in the eCRF and reported regardless of study period

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

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

The AE grading scale used will be the NCI CTCAE. A copy of the grading scale can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.cancer.gov). CRS events will be reported using the grading scale outlined in the axicabtagene ciloleucel IB (as modified from Lee, et al, 2014). The severity of neurologic toxicities will be graded using the NCI CTCAE. The severity of individual signs/symptoms of CRS and neurologic toxicities will be graded according to the NCI CTCAE for those signs/symptoms that are not part of the grading scale.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) axicabtagene ciloleucel, 2) utomilumab, 3) conditioning chemotherapy, 4) any protocol-required study procedure or treatment, 5) disease progression, 6) concurrent disease, 7) concomitant medication, or 8) other.

The relationship is indicated by a "related" or "not related" response and entered in the eCRF. In assessing causality, the investigator or qualified subinvestigator will use clinical judgment and the following considerations:

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

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

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

9.2.1. Reporting Abnormal Laboratory Findings

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values.

In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

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

- 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

9.2.2. Abnormal Liver Function Tests (Hy's Law): Drug-induced Liver Injury

Elevated ALT or AST (> 3 x ULN), in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia, is considered to be an indicator of severe liver injury (ie, drug-induced liver injury [DILI]). Therefore, investigators must report the following events as SAEs:

- ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN (of which 35% is direct bilirubin)
- ALT or AST > 3 x ULN in combination with clinical jaundice

9.2.3. AEs of Special Interest (Immediately Reportable to the Sponsor)

Investigators must report the following AEs of special interest to the sponsor no more than 24 hours after learning of the event:

- DILI is defined in Section 9.2.2. A risk management plan associated with utomilumab requires that any DILI is reported as an AE under expedited timelines.

- Any DILI occurring between the first infusion of utomilumab and 30 days after completing the final dose of utomilumab must be reported within 24 hours.
- CRS events Grade 3 or higher *(by modified Lee criteria)*
- Neurologic events Grade 3 or higher *(by CTCAE)*
- All events of cerebral edema
- All events of hemophagocytic lymphohistiocytosis/macrophage activation syndrome

9.3. Definition of Serious Adverse Events

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

- Fatal
- Life-threatening (ie, an event that places the subject at immediate risk of death); it does not refer to an event that hypothetically might have caused death if it were more severe
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event. If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event."

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

Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE according to NCI CTCAE criteria; the event itself may be of relatively minor medical significance and, therefore, may not meet the seriousness criteria. Severity and seriousness need to be independently assessed for each AE recorded on the electronic CRF (eCRF).

9.4. Reporting of SAEs

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through the 30 days after completing

the final dose of utomilumab or 12 weeks after the axicabtagene ciloleucel infusion, whichever is longer. After this follow-up period has been completed, only targeted SAEs will be reported. Targeted SAEs are defined as and include neurological, hematological, infections, GVHD and autoimmune disorders, and secondary malignancies that occur up to 24 months or until disease progression. After 24 months, targeted SAEs of secondary malignancies will continue to be reported through 15 years after axicabtagene ciloleucel infusion and will be recorded in the eCRF.

SAEs, which the investigator assesses as related to axicabtagene ciloleucel or utomilumab, including all deaths that occur from signing of the screening ICF should be reported regardless of the time period. Refer to Section 9.5 for instructions on reporting deaths.

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

The following must be submitted to Kite via the eSAE system within 24 hours of the investigator's knowledge of the event:

- All SAEs
- Pregnancy or lactation exposure as defined in Section 9.7
- AEs of special interest as defined in Section 9.2.3

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, SAEs will be entered into the eSAE system once it becomes available.

All SAEs will be reported to the health authorities per local reporting guidelines.

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded on the CRF as AEs or SAEs and indicated as being due to disease progression. If the malignancy has a fatal outcome before 24 months, then the event "B-cell lymphoma" must be recorded as an SAE with the outcome being fatal.

Death must be reported if it occurs during the SAE reporting period, irrespective of any intervening treatment. Refer to Section 9.5 for instructions on reporting deaths associated with the underlying malignancy/disease progression.

Any death occurring after enrollment and prior to the post-treatment follow-up period, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the post-treatment follow-up period requires expedited reporting within 24 hours only if it is considered related to treatment, axicabtagene ciloleucel, utomilumab, and/or study-required treatments (eg, lymphodepleting chemotherapy).

Following completion of KTE-C19-111, 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 (within the 30 days after completing the final dose of utomilumab or 12 weeks after the axicabtagene ciloleucel infusion, whichever is longer) 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. Any death occurring after the signing of the main study ICF within the AE reporting period and regardless of attribution to treatment, requires expedited reporting within 24 hours after the investigator's knowledge of the event. Any death occurring after the AE reporting period requires expedited reporting within 24 hours only if it is considered related to treatment, axicabtagene ciloleucel infusion, utomilumab, and/or study-required treatments (eg, lymphodepleting chemotherapy).

Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy).

9.6. Diagnosis versus Signs and Symptoms

For AEs, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the AE form. The exception is for CRS where both the diagnosis and the signs and symptoms comprising CRS will be captured on the CRF AE form. For situations when an AE or SAE is due to the disease under investigation, report the signs and symptoms of the AE or SAE. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

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%) through at least 90 days after the last dose of utomilumab or for at least 6 months after axicabtagene ciloleucel infusion or conditioning chemotherapy dosing (whichever occurs later). Male subjects are recommended to

not father a child for at least 90 days after the last dose of utomilumab or for at least 6 months after completion of axicabtagene ciloleucel infusion or conditioning chemotherapy dosing (whichever occurs later). Refer to Appendix 3 for a complete list of highly effective contraception methods.

If a pregnancy occurs in either a female subject enrolled into the study any time after axicabtagene ciloleucel infusion, within 6 months after conditioning chemotherapy, or within 90 days after the last dose of utomilumab, whichever is longer, or in a female partner of a male subject within 6 months of axicabtagene ciloleucel infusion or completing the conditioning chemotherapy or within 90 days after the last dose of utomilumab, whichever is longer, the pregnancy must be reported using the Pregnancy Reporting Form within 24 hours of the investigator's knowledge of the pregnancy event.

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 or 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. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

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

Pregnancies of female partners of male study subjects exposed to protocol-required therapies must also be reported and relevant information should be submitted to Kite Patient Safety and Pharmacovigilance 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 Kite Patient Safety and Pharmacovigilance.

All such pregnancies must be reported to Kite Patient Safety and Pharmacovigilance using the Pregnancy Report Form within 24 hours after becoming aware of the pregnancy. Information regarding the pregnancy and/or outcome will be requested by the sponsor. Pregnancy Report Forms should be reported to Kite Patient Safety and Pharmacovigilance at PPD or fax: PPD.

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 6 months. Report the lactation case and Special Situations Reporting Forms to Kite Patient Safety and Pharmacovigilance at PPD or fax: PPD.

9.8. Hospitalization and Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be SAEs:

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

9.9. Abnormal Vital Sign Values

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

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

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

9.10. Safety Review Team and Dose-limiting Toxicity

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 and review of SAEs.

Dose-limiting toxicity is defined as the following axicabtagene ciloleucel- or utomilumab-related events with an onset from immediately after and through 28 days following the first utomilumab infusion:

- Grade 4 hematologic toxicity lasting more than 30 days (except lymphopenia or B-cell aplasia)

- All axicabtagene ciloleucel- or utomilumab-related Grade 3 non-hematologic toxicities lasting for > 7 days and all axicabtagene ciloleucel- or utomilumab-related Grade 4 non-hematologic toxicities regardless of duration are considered DLTs, with the exception of the following, which are not considered DLTs:

  — Aphasia/dysphasia or confusion/cognitive disturbance, which resolves to at least Grade 1 within 2 weeks and to at least baseline within 4 weeks

  — Fever of any grade

  — Immediate IP-related hypersensitivity reactions occurring within 2 hours of cell or utomilumab infusion that are reversible to a Grade 2 or less within 24 hours or administration with standard therapy

  — Renal toxicity, which requires dialysis for ≤ 7 days

  — Intubation for airway protection if ≤ 7 days

  — Tumor lysis syndrome (TLS), including associated manifestations attributable to TLS (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 nausea and/or anorexia

CRS will be graded according to a modified grading system {Lee 2014} as described in the current axicabtagene ciloleucel IB. AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. Consistent with non-CRS toxicities, all occurrences of Grade 3 CRS of duration > 7 days and all occurrences of Grade 4 CRS are considered DLTs, other than occurrences of CRS due to the exceptions listed above.

During Phase 1, approximately 3 to 36 subjects with large B-cell lymphoma will be enrolled to evaluate the safety of axicabtagene ciloleucel and utomilumab regimens.

Subjects in each cohort will be evaluated for DLTs within the first 28 days following the completion of their first dose of utomilumab. The analysis of DLTs will be based on the incidence of DLT and overall safety profile of the axicabtagene ciloleucel and utomilumab regimen. If the subject incidence of DLT is 0 of 3 subjects, the study will proceed to the next cohort or if specific to Cohort 5, the study may proceed to Phase 2 of the trial. This decision will be based on overall benefit/risk and available biomarker data.

However, if 1 of the 3 enrolled subjects within any cohort present with a protocol-defined DLT during Phase 1, the SRT may recommend enrolling an additional set of 3 subjects (up to 6 subjects in total) at the same dose that was administered in the first 3 subjects in that cohort. In this scenario, progression to the next cohort or to Phase 2 of the study will proceed if 1 of the first 6 subjects presents with a DLT.

If the subject incidence of DLT is $\geq 2/6$, other axicabtagene ciloleucel and utomilumab regimens, including different doses of utomilumab, may be explored in collaboration with the SRT in an additional 3 to 6 subjects (Figure 5). The same DLT rules apply as previously described.

At the conclusion of each SRT safety review meeting, the SRT will make recommendations on further study conduct. The SRT will make a recommendation from among the following:

- Enroll additional subjects for that dosing cohort
- Continue evaluation of additional regimens as specified in the study protocol
- Change in study conduct
- Proceed to Phase 2
- Terminate study

Additional axicabtagene ciloleucel and utomilumab regimens not currently specified in the protocol may also be explored in Phase 1 at the recommendation of the SRT, following a protocol amendment. Lastly, the SRT may decide to halt escalation of the utomilumab dose levels at the time of each SRT meeting after review of the data, even in the absence of DLT, if it deems no further benefit would be derived with higher doses of utomilumab.

As part of its oversight of the study, the SRT will also meet 1 time after 6 subjects have been treated with axicabtagene ciloleucel and utomilumab in the Phase 2 portion of the study and have completed the Week 4 disease assessment. The SRT will review safety and efficacy data and will be chartered to make trial conduct recommendations based on an analysis of benefit/risk ratio. The SRT may meet more often as needed.

For both Phase 1 and Phase 2 portions of the study, in cases where a consensus recommendation is not reached by the SRT, the Sponsor will serve as the final decision-making body for further study conduct.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in subjects with relapsed/refractory large B-cell lymphoma treated with the axicabtagene ciloleucel followed by utomilumab.

10.2. Study Endpoints

10.2.1. Primary Endpoints

- Phase 1: Incidence of AEs defined as DLTs.
- Phase 2: Complete response rate (CR per the Lugano Classification {Cheson 2014}), as determined by the study investigators.

10.2.2. Secondary Endpoints

Secondary endpoints are applicable to both Phase 1 and Phase 2:

- Objective response rate: Objective response rate is defined as the incidence of either a CR or a PR per Lugano Classification {Cheson 2014} as determined by study investigators. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.
- Duration of response: Among subjects who experience an objective response, DOR is defined as the date of their first objective response to disease progression per Lugano Classification {Cheson 2014}, as determined by study investigators, or death from any cause. Data from the retreatment period will not be included for analysis. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date, and their response will be noted as ongoing. Subjects who receive additional anti-cancer therapy in the absence of documented progression will be censored at the last evaluable disease assessment prior to the additional therapy. Subjects who receive SCT in the absence of documented 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 SCT are included in the derivation of DOR.
- Progression-free survival: Progression-free survival (PFS) is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per Lugano Classification {Cheson 2014}, as determined by study investigators, or death from any cause. Data from the retreatment period will not be included for analysis. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date. The PFS for subjects who undergo SCT while in

remission will be censored at the last evaluable disease assessment prior to the date of SCT; the PFS for subjects who undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A sensitivity analysis will be conducted in which disease assessments obtained after SCT are included in the derivation of PFS.

- Overall survival: OS is defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last date known as alive.
- Incidence of AEs and clinically significant changes in safety lab values
- Pharmacokinetics: Levels of axicabtagene ciloleucel in blood
- Pharmacodynamics: Levels of cytokines in serum

CCI [redacted]

[redacted]

[redacted]

10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 3 to 60 subjects.

Phase 1 will enroll approximately 3 to 36 subjects. If the study proceeds to Phase 2, a total of up to 24 additional subjects will be enrolled.

This study uses a single-arm design to estimate the true complete response rate in subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel and utomilumab at the dosing schedule tested in Phase 1 and deemed safe by the SRT. With a total sample size of approximately 27 subjects at a given dosing schedule, of which at least 3 will have been treated in the Phase 1 portion, an observed CR rate of 70% will yield an exact 95% confidence interval (CI) of (50%, 86%). This target CR rate, and the lower limit of the 70% CI for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with relapsed/refractory large B-cell lymphoma over existing therapies.

Additional assumptions and corresponding two-sided 95% and 80% exact CIs are provided in Table 8.

Table 8. Exact Confidence Intervals (95% and 80%) Corresponding to Observed CR Rate Following Treatment of 27 Subjects with Axicabtagene Ciloleucel and Utomilumab

Subjects with CR	Observed CR Rate	95% Confidence Interval	80% Confidence Interval
15	56%	[35%, 75%]	[42%, 69%]
17	63%	[42%, 81%]	[49%, 76%]
19	70%	[50%, 86%]	[56%, 82%]
21	78%	[58%, 91%]	[64%, 88%]
23	85%	[66%, 96%]	[73%, 93%]

Abbreviations: CR, complete response.

10.4. Interim Analysis and Early Stopping Guidelines

Formal interim analyses of efficacy are not planned for the early trial stopping purpose.

10.4.1. Safety Interim Analysis

An SRT will be chartered to review safety during Phase 1 of the study only and to make recommendations on further study conduct in Phase 1 and progression to Phase 2.

The SRT will additionally meet on at least one occasion during the Phase 2 portion of the study after 6 subjects have completed their 1-month disease assessment. The SRT will review safety and efficacy data and will be chartered to make trial conduct recommendations based on an analysis of benefit vs risk.

10.5. Analysis Subsets

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

Modified intent-to-treat set (mITT): The mITT will consist of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel, 2 x 10^6 CAR T cells/kg (range 1 x 10^6 to 2.4 x 10^6 CAR T cells/kg), and at least 1 dose of utomilumab as determined upon completion of the Phase 1 and Phase 2 portions of the study. This analysis set will be used for all efficacy analyses.

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

The DLT evaluable set: The DLT evaluable set will consist of all subjects in each Phase 1 cohort who are treated with axicabtagene ciloleucel and at least 1 dose of utomilumab who either:

- Received the target axicabtagene ciloleucel dose and were followed for at least 28 days after the first utomilumab infusion
- Received a dose of anti-CD19 CAR T cells lower than the target for that cohort and a subsequent utomilumab infusion and experienced a DLT during the 28-day, post-utomilumab infusion period

10.6. Planned Method of Analysis

The primary analysis will be performed when the last treated subject in the mITT set has had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment. The final analysis will occur when all subjects have completed the study.

10.6.1. Complete Response Rate

The incidence of complete response and exact 2-sided 95% CIs will be generated.

10.6.2. Objective Response Rate

The incidence of objective response and exact 2-sided 95% CIs will be generated.

10.6.3. Duration of Response

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

10.6.4. Progression-free Survival

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

10.6.5. Overall Survival

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

10.6.6. Safety

Subject incidence rates of AEs, including all, serious, fatal, CTCAE 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. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

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

10.6.7. Long-term Data Analysis

All subjects will be followed for survival status for up to approximately 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

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

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

11.1. Independent Review Board/Independent Ethics Committee

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

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

During the course of the study, investigators 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 maintained within all material that is submitted to the key sponsor contact. The following rules are to be applied.

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

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

Per country-specific regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, Contract Research Organization (CRO), IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which 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 Pharma, Inc., based on the following criteria:

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

12. PROTOCOL AMENDMENTS AND TERMINATION

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

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

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

13. STUDY DOCUMENTATION AND ARCHIVING

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

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

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

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

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

14. STUDY MONITORING AND DATA COLLECTION

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

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

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

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

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

15. PUBLICATION

Authorship of publications from data generated in KTE-C19-111 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states that authorship should be based on:

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

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

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

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

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17. APPENDICES

Appendix 1. Sponsor and Investigator Signature Page

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

A PHASE 1/2 MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL IN COMBINATION WITH UTOMILUMAB IN SUBJECTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA (ZUMA-11)

Version 5.0, 07 June 2022

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

PPD

Kite Medical Monitor Name (Printed)

08-Jun-2022

Date

PPD

INVESTIGATOR STATEMENT

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

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

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

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Lugano Classification {Cheson 2014}

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

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

Complete Remission:

Complete Metabolic Response (CMR) for Positron Emission Tomography-Computed Tomography (PET-CT)-Based Response

The designation of CMR requires all of the following:

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

Complete Radiologic Response (CRR) for Computed Tomography (CT)-Based Response

The designation of CRR requires all of the following:

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

Partial Remission:

Partial Metabolic Response (PMR) for PET-CT-Based Response

The designation of PMR requires all of the following:

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

  Note:

  — At interim, these findings suggest responding disease

  — At end of treatment, these findings suggest residual disease

  — No new sites of disease should be observed

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

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

Partial Radiologic Response (PRR) for CT-Based Response

The designation of PRR requires all of the following:

- ≥ 50% decrease in sum of the product of the perpendicular diameters (SPD) of up to 6 target measurable nodes and extranodal sites
- When a lesion is too small to measure on CT, assign 5 x 5 mm as the default value
- When no longer visible, 0 x 0 mm
- For a node > 5 x 5 mm, but smaller than normal, use the actual measurement for calculation
- Absent/normal, regressed, but no increase of non-measured lesions
- Spleen must have regressed by > 50% in length beyond normal
- No new sites of disease should be observed.

Stable Disease:

No Metabolic Response (NMR) for PET-CT-Based Response

The designation of NMR requires all of the following:

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

Stable Radiologic Disease (SRD) for CT-Based Response

The designation of SRD requires all of the following:

- < 50% decrease from baseline in the SPD 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 (PMD) for PET-CT-Based Response

The designation of PMD requires at least 1 of the following:

- A 5PS score of 4 or 5 with an increase in intensity of uptake from baseline
- 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 or 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 (PRD) for CT-Based Response

The designation of PRD requires at least 1 of the following:

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

Appendix 3. Childbearing Potential and Birth Control

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

A. Definition of Childbearing Potential

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

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

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

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

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. Such methods include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[1] via the following form of administration:
  - — Oral
  - — Intravaginal
  - — Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - — Oral
  - — Injectable
  - — Implantable[2]

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

- Intrauterine device)[2]
- Intrauterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

C. Unacceptable Birth Control Methods

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

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

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.