# CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1) |
| **Protocol Number:** | KTE-C19-101 |
| **IND Number:** | 016278 |
| **EudraCT Number:** | 2015-005007-86 |
| **Clinical Study Sponsor:** | Kite Pharma, Inc.<br>2400 Broadway<br>Santa Monica, CA 90404<br>United States of America |
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| **Version:** | 1.0 (Amendment # **8**) |
| **Date:** | **11 February** 2019 |

## Confidentiality Notice

## INVESTIGATOR'S AGREEMENT

I have read the attached protocol titled: A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL) (ZUMA-1) dated **11 Feb 2019** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines.

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

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

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

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Signature

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Name of investigator

_____

Date

## PROTOCOL SYNOPSIS

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| **Title** | A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). |
| **Indication** | The indication is for the treatment of adult subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), transformed follicular lymphoma (TFL), and high grade B-cell lymphoma (HGBCL) after two or more lines of systemic therapy. |
| **Study Design** | Study KTE-C19-101 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). The trial will be separated into 3 distinct phases designated as the Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**).<br><br>Phase 1 Study<br><br>During Phase 1 study, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 pivotal study as depicted in Figure 3 and outlined in Section 9.10.<br><br>Phase 2 Pivotal Study<br><br>In the Phase 2 pivotal study, approximately 92 subjects will enroll into 2 separate cohorts designated as Cohort 1 and Cohort 2:<br><br>• Cohort 1 will enroll approximately 72 adult subjects with refractory DLBCL.<br><br>• Cohort 2 will enroll approximately 20 adult subjects with refractory PMBCL and TFL. TFL is defined as subjects who received prior therapy for follicular lymphoma. |

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| | Phase 2 Safety Management Study<br>In the Phase 2 safety management study (SMS), approximately **170** subjects will enroll into **4** separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**.<br>• Cohort 3 will enroll approximately 40 adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, or TFL.<br>• Cohort 4 will enroll and dose approximately 40 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL or HGBCL after **2** or more lines of systemic therapy.<br>• Cohort 5 will enroll and dose approximately 50 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL or HGBCL after 2 or more lines of systemic therapy.<br>• **Cohort 6 will enroll and dose approximately 40 adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 or more lines of systemic therapy.**<br>Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:<br>• Screening<br>• Enrollment/Leukapheresis period<br>• Bridging therapy (if applicable; safety management study only) or debulking therapy (if applicable, safety management study, Cohort 5 only)<br>• Conditioning chemotherapy period<br>• Investigational product (IP) treatment period<br>• Post-treatment assessment period<br>• Long-term follow-up period<br>For study requirements assigned to each study period, refer to Section 7 for details. |
| **Study Objectives** | Phase 1 Study<br>The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel regimens.<br>Phase 2 Pivotal Study<br>The primary objective of the Phase 2 pivotal study is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR) in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints. |

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| | Phase 2 Safety Management Study<br><br>The primary objective of the Phase 2 safety management study is to assess the impact of prophylactic regimens, earlier interventions, tumor debulking, **and prophylactic steroid use** on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicity. Secondary objectives will include assessment of efficacy, levels of anti-CD19 chimeric antigen receptor (CAR) T cells, cytokines in blood/serum, and the change in European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6. |
| **Study Hypothesis and Endpoints** | Phase 1 Study<br><br>Primary Endpoint<br><br>• Incidence of adverse events defined as dose-limiting toxicities (DLT)<br><br>Secondary Endpoints<br><br>• Objective response rate (complete response [CR] + partial response [PR]) per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma<br>• Duration of response (DOR)<br>• Overall survival (OS)<br>• Progression-free survival (PFS)<br>• Incidence of adverse events and clinical significant changes in safety lab values<br>• Incidence of adverse events and clinical significant changes in safety lab values<br>• Levels of anti-CD19 CAR T cells in blood<br>• Levels of cytokines in serum<br>• Incidence of anti-axicabtagene ciloleucel antibodies<br><br>Exploratory Endpoints<br><br>• Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) and duration of second response among subjects retreated with axicabtagene ciloleucel (Cheson et al, 2007)<br>• Objective response rate and DOR as determined by IWG Response Criteria for Malignant Lymphoma<br>• Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product |

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| | Phase 2 Pivotal Study<br><br>This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the objective response rate to axicabtagene ciloleucel in Cohort 1 and Cohort 2 is significantly greater than 20%.<br><br>Primary Endpoint<br><br>• Objective response rate (CR + PR) per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by study investigators.<br><br>Secondary Endpoints<br><br>• Objective response rate per Independent Radiology Review Committee (IRRC)<br><br>• DOR<br><br>• PFS<br><br>• OS<br><br>• Incidence of adverse events and clinical significant changes in safety lab values<br><br>• Levels of anti-CD19 CAR T cells in blood<br><br>• Levels of cytokines in serum<br><br>Incidence of anti-axicabtagene ciloleucel antibodies<br><br>Exploratory Endpoint(s) for Phase 2 Pivotal Study<br><br>• Objective response rate (CR + PR) per revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) and duration of second response among subjects retreated with axicabtagene ciloleucel<br><br>• Objective response rate and DOR as determined by IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2014)<br><br>• Investigation of potential biomarker development based on assessment of blood cells, tumor cells and the proposed actions of the investigational product |

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| | Phase 2 Safety Management Study<br>No hypothesis will be tested in Cohort 3, Cohort 4**,** Cohort 5, **and Cohort 6**.<br>Primary Endpoint<br>• **Incidence** and severity of CRS and neurologic toxicities.<br>Secondary Endpoints<br>• Objective response rate (complete response [CR] + partial response [PR]) per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by study investigators.<br>• DOR<br>• PFS<br>• OS<br>• Incidence of adverse events and clinically significant changes in safety lab values<br>• Levels of anti-CD19 CAR T cells in blood<br>• Levels of cytokines in blood<br>• Incidence of anti-axicabtagene ciloleucel antibodies<br>• Changes over time in the EQ-5D scale score and visual analogue scale (VAS) score (Phase 2 SMS only)<br>Exploratory Endpoints<br>• **Biomarkers** based on assessment of blood cells, tumor cells, and the proposed actions of the investigational product |
| **Sample Size** | Approximately **268** to **286** subjects<br>Phase 1 Study: approximately 6 to 24 subjects<br>Phase 2 Pivotal Study: approximately 92 subjects enrolled into 2 cohorts<br>• Cohort 1: approximately 72 subjects<br>• Cohort 2: approximately 20 subjects<br>Phase 2 Safety Management Study: approximately **17**0 subjects enrolled and dosed within **4** cohorts<br>• Cohort 3: approximately 40 subjects<br>• Cohort 4: approximately 40 subjects<br>• Cohort 5: approximately 50 subjects<br>• **Cohort 6: approximately 40 subjects** |

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| **Study Eligibility** | Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria for both phases of the study. |
| **Treatment** | Investigational Product:<br>• Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x $10^8$ anti-CD19 CAR T cells will be administered. Under circumstances where subjects initially respond and subsequently relapse, subjects may be eligible for a second course of conditioning chemotherapy and axicabtagene ciloleucel. Refer to Section 6 for treatment and Section 7.13.9 for retreatment details.<br>Bridging Therapy (Phase 2 Safety Management Study)<br>• At the discretion of the investigator, bridging therapy may be considered for subjects particularly with high disease burden at screening or baseline assessment (eg, bulky disease or rapidly progressing disease).<br>• For subjects receiving bridging therapy, refer to Section 6 for bridging therapy details.<br>Debulking Therapy (Phase 2 Safety Management Study, Cohort 5)<br>• Debulking therapy should be applied to all subjects enrolled in Cohort 5 with the aim of reducing lymphoma burden. Debulking therapy is to be administered after leukapheresis and prior to administration of conditioning chemotherapy or axicabtagene ciloleucel.<br>• Refer to Section 6.2.2 for debulking therapy details<br>Conditioning Chemotherapy<br>• Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/$m^2$/day and cyclophosphamide 500 mg/$m^2$/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.<br>Additional axicabtagene ciloleucel regimens may be explored in Phase 1 per Section 9.10. |

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| | Phase 2 Safety Management Study<br>• Subjects assigned to Cohort 3 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above and will also receive prophylactic tocilizumab and levetiracetam for toxicity management as outlined in Section 6.3.4 and Section 6.4.<br>• Subjects assigned to Cohort 4 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above, but toxicity management will intervene at lower grades of CRS and neurologic toxicities as outlined in Section 6.4.1.<br>• Subjects assigned to Cohort 5 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as other safety management cohorts; toxicity management will be completed as outlined in Section 6.4.2.<br>• **Subjects assigned to Cohort 6 will receive the same conditioning chemotherapy and axicabtagene ciloleucel regimen as described above and will receive prophylactic steroids; toxicity management will intervene at lower grades of CRS and neurologic toxicities as outlined in Section 6.4.1.** |
| **Procedures** | At specific time points as outlined in the schedule of assessments, subjects will undergo the following assessments/procedures: collection of informed consent, general medical history including previous treatments for NHL, physical exam including vital signs and performance status, neurologic assessments, blood draws for complete blood count (CBC), chemistry panels, cytokines, C-reactive protein, lymphocyte subsets, anti-axicabtagene ciloleucel antibodies, replication-competent retrovirus (RCR) and anti-CD19 CAR T cell analysis. Women of childbearing potential will undergo a urine or serum pregnancy test.<br>Subjects will also undergo a baseline electrocardiogram (ECG), echocardiogram (ECHO), brain magnetic resonance image (MRI), a positron emission tomography–computed tomography (PET-CT), possible bone marrow aspirate/biopsy and leukapheresis.<br>Subjects assigned to Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** will complete the EQ-5D questionnaire at baseline and after axicabtagene ciloleucel (see Section 7.4 and schedule of assessments [SOA]) infusion and will have lumbar punctures performed for the collection of **cerebrospinal fluid (**CSF**)** (see Section 7.9 and SOA) before and after axicabtagene ciloleucel infusion.<br>Routinely throughout the conduct of the study, subjects will be asked to report concomitant medications and adverse events and will have their disease assessed. |

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| **Safety Review Team and Data Safety Monitoring Board** | An SRT, that is internal to the study sponsor and in collaboration with at least one study investigator, will review safety data in Phase 1 of the study. The SRT will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10.<br><br>Phase 2 Pivotal Study: An independent Data Safety Monitoring Board (DSMB) will meet when 20 and 50 subjects in the modified intent-to-treat (mITT) set of Cohort 1 have had the opportunity to complete their 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.<br><br>Phase 2 Safety Management Study: The DSMB will meet to review Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** safety data when 20 subjects in each cohort have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. The DSMB may meet more often as needed. Refer to Section 9.11 and Section 9.12. |
| **Statistical Considerations** | Phase 1 Study<br><br>The primary endpoint for the Phase 1 study is the incidence of DLT.<br><br>Phase 2 Pivotal Study<br><br>The primary endpoint for the Phase 2 pivotal study (Cohort 1 and Cohort 2) of the study is objective response rate per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by the study investigators. This endpoint will be based on a modified intent-to-treat (mITT) population consisting of all subjects enrolled and treated with axicabtagene ciloleucel at a dose of at least $1 \times 10^6$ anti-CD19 CAR T cells/kg.<br><br>This study uses a single-arm design to test for an improvement in response rate in the DLBCL cohort (n = 72) and in Cohorts 1 and 2 combined (n = 92). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.<br><br>The overall 1-sided alpha level of 0.025 will be divided between the inference in Cohort 1 and the inference in Cohorts 1 and 2 combined using the methodology described in Song et al and Wang et al (Moye and Deswal 2001; Song and Chi 2007; Wang et al, 2007). The objective response for Cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response rate in Cohort 1 and 2 combined will be tested at a 1-sided alpha level of 0.0075. |

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| | Within Cohort 1, two interim and one primary analyses will be performed.<br>• Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only.<br>• Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early demonstration of efficacy.<br>• The primary analysis of Cohort 1 will occur after 72 subjects in the mITT set have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion.<br>Accrual to the study will continue during interim analysis 1 and interim analysis 2 of Cohort 1.<br>For Cohort 1 and Cohort 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set in Cohort 1 and 20 subjects in the mITT set in Cohort 2 have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion.<br><u>Phase 2 Safety Management Study</u><br>The primary objective of Cohort 3 is to assess the impact of prophylactic regimens on the rate and severity of CRS and neurologic toxicities.<br>The primary objective of Cohort 4 is to assess the impact of earlier interventions on the incidence and severity of CRS and neurologic toxicities.<br>The primary objective of Cohort 5 is to assess the impact of debulking therapy on the incidence and severity of CRS and neurologic toxicities.<br>**The primary objective of Cohort 6 is to assess the impact of prophylactic steroid use and earlier interventions on the incidence and severity of CRS and neurologic toxicities.**<br>The secondary objectives of Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** include **assessment** of efficacy endpoints (ORR, DOR, PFS, OS) and levels of anti-CD19 CAR T cells and cytokines in the blood.<br>**Analyses** of the safety and efficacy endpoints of this portion of the study will be entirely descriptive, with no formal statistical testing being performed. |

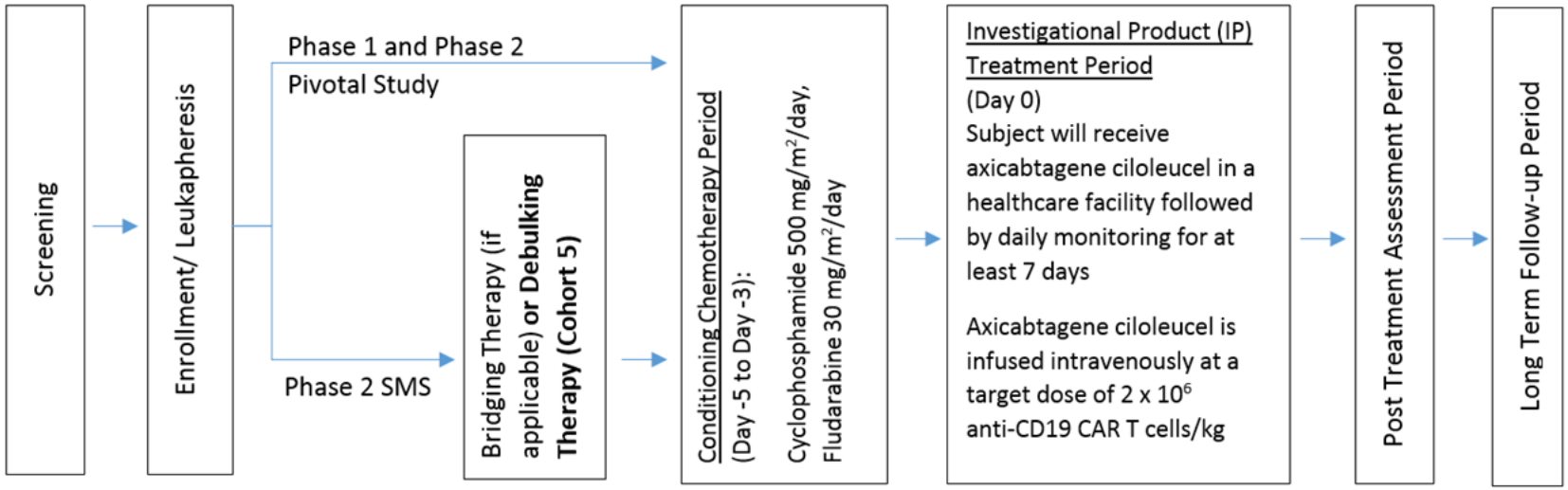
# STUDY GLOSSARY

| Abbreviation or Term | Definition/Explanation |
|---|---|
| AE | Adverse event |
| ALL | Acute lymphoblastic leukemia |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ASCT | Autologous stem cell transplant |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BBB | Blood brain barrier |
| BUN | Blood urea nitrogen |
| CAR | Chimeric antigen receptor |
| CBC | Complete blood count |
| CLL | Chronic lymphocytic leukemia |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CPF | Cell processing facility |
| CR | Complete response |
| CRF | Case report form |
| CRP | C-reactive protein |
| CRS | Cytokine release syndrome |
| CSF | Cerebrospinal fluid |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLBCL | Diffuse large B-cell lymphoma |
| DLT | Dose-limiting toxicity |
| DOR | Duration of response |
| DSMB | Data Safety Monitoring Board |
| eACT™ | Engineered autologous cell therapy |
| EBV | Epstein-Barr virus |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EQ-5D | European Quality of Life-5 Dimensions |
| FAS | Full analysis set |
| FL | Follicular lymphoma |
| GCP | Good Clinical Practice |
| GOT | Glutamic-oxaloacetic transaminase |
| GPT | Glutamic-pyruvic transaminase |
| HGBCL | High grade B-cell lymphoma |
| HIV | Human immunodeficiency virus |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| HLH | Hemophagocytic lymphohistiocytosis |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| ICU | Intensive care unit |
| ID | Identification |
| IP | Investigational product |
| IRB/IEC | Institutional Review Board/Independent Ethics Committee |
| IRRC | Independent Radiological Review Committee |
| IV | Intravenous |
| IWG | International Working Group |
| LDH | Lactate dehydrogenase |
| LTFU | Long-term follow-up |
| LVEF | Left ventricular ejection fraction |
| mITT | Modified intent-to-treat |
| MMSE | Mini-Mental Status Exam |
| MRI | Magnetic resonance imaging |
| MSGV1 | Murine stem cell virus-based vector |
| NaCl | Sodium chloride |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin lymphoma |
| 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 |
| PMBCL | Primary mediastinal B-cell lymphoma |
| PR | Partial response |
| RCR | Replication-competent retrovirus |
| qPCR | Quantitative polymerase chain reaction |
| SAE | Serious adverse event |
| scFv | Single-chain variable fragment |
| SD | Stable disease |
| SMS | Safety management study |
| SOA | Schedule of assessment |
| SPD | Sum of the product of diameters |
| SRT | Safety review team |
| SUSAR | Suspected unexpected serious adverse reaction |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| Study Day 0 | Defined as the first day that axicabtagene ciloleucel is administered to the subject |
| TFL | Transformed follicular lymphoma |
| ULN | Upper limit of normal |
| VAS | Visual analogue scale |
| WBC | White blood cell |

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




Study KTE-C19-101 is a Phase 1-2 single-arm, open-label, multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory DLBCL, PMBCL and TFL. During Phase 1, approximately 6-24 subjects with DLBCL, PMBCL or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10.

Upon SRT recommendation, the pivotal Phase 2 will commence and enroll subjects into 2 separate cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL. Refer to entrance criteria for TFL eligibility requirements.

Upon completion of enrollment of the Phase 2 pivotal study, the Phase 2 Safety Management Study will commence and enroll subjects into **4** separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**.

- Cohort 3 will enroll adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, and TFL.
- Cohort 4 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL and HGBCL after 2 systemic lines of therapy.
- Cohort 5 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy**.**
- **Cohort 6 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.**

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will follow through the following study periods: a screening period, an enrollment/leukapheresis period, a conditioning chemotherapy period, an IP treatment period, a post treatment assessment period and a long term follow-up period.

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# 1. OBJECTIVES

The primary objective of Phase 1 study is to evaluate the safety of axicabtagene ciloleucel regimens.

The primary objective of Phase 2 pivotal study is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR) in subjects with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints.

The primary objective of the Phase 2 safety management study is to assess the impact of a prophylactic regimen, earlier interventions, debulking therapy**, or prophylactic steroid use** on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicities. The key secondary objectives include assessment of efficacy, levels of anti-CD19 chimeric antigen receptor (CAR) T cells, cytokines in blood/serum, and the change in European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

# 2. DISEASE BACKGROUND AND RATIONALE

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of cancers originating in B lymphocytes, T lymphocytes or natural killer cells. In the United States, B cell lymphomas represent 80-85% of cases reported. In 2013, approximately 69,740 new cases of NHL and over 19,000 deaths related to the disease were estimated to occur. Non-Hodgkin lymphoma is the most prevalent hematological malignancy and is the seventh leading site of new cancers among men and women and account for 4% of all new cancer cases and 3% of deaths related to cancer (Howlader et al, 2017). Large B-cell lymphomas represent the most common sub-group of NHL (Rodriguez-Abreu et al, 2007).

## 2.1. Diffuse Large B-cell Lymphoma

DLBCL is the most common subtype of large B-cell lymphoma, 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 two decades, progress has been made in understanding the biological heterogeneity of DLBCL and in improving survival with combinations of CHOP and immunotherapy. The addition of rituximab into combination therapies for DLBCL have greatly improved patient outcomes. However, patients with chemotherapy-refractory DLBCL following treatment under the current standards of care still have a particularly dire prognosis, with no curative treatment options (Flowers et al, 2010).

The population with the highest unmet need continues to consist of patients who do not respond to first line combination chemotherapy (typically R-CHOP) or who do not respond to their last course of combination chemotherapy, as the disease is mostly insensitive to subsequent combination chemotherapy (typically R-ICE, R-ESHAP) (Table 1). In a review of 64 patients with DLBCL with disease progression during first line chemotherapy or only transient response (≤90 days) after end of induction treatment, the response rate to second line therapy was 15% and the median overall survival (OS) was 6 months, and no patient survived more than 26 months after first diagnosis (Josting et al, 2000). An analysis of outcome in 1126 patients with DLBCL after first line R-CHOP included 33 patients with primary refractory DLBCL who received second line therapy with curative intent. Only 3 (9%) patients were able to receive autologous stem cell transplantation (ASCT), and only 1 (3%) patient achieved long term survival (Hitz et al, 2010). Seshadri et al analyzed 120 patients who did not respond to second line platinum-based chemotherapy regimens (e.g., R-ICE) and showed that only 14% responded to their third line therapy (Seshadri et al, 2008). Ardeshna et al followed 19 patients with large B-cell lymphoma, and 9 patients with TFL who did not respond to second line chemotherapy. Only 5 of the 28 total patients (18%) responded to third line chemotherapy (Ardeshna et al, 2005).

**Table 1. Historical Responses in Refractory NHL (SD or PD to Last Line of Therapy)**

| Setting | Outcome to Subsequent Therapy |
|---|---|
| **Refractory to 1st line** | |
| (Philip et al, 1995) | ORR 21% |
| (Josting et al, 2000) | ORR 15%, median OS 6 mos |
| (Ardeshna et al, 2005) | ORR 0% |
| (Hitz et al, 2010) | Proceeded to ASCT 9%, 3% survived > 1 year |
| (Telio et al, 2012) | ORR 23%, median OS 10 mos |
| (Matasar et al, 2013) | ORR 10% |
| Refractory to 2nd line | |
| (Moskowitz et al, 1999) | Median OS 5 mos |
| (Ardeshna et al, 2005) | ORR 18%, median OS (large B-cell lympohoma) <6 mos |
| (Seshadri et al, 2008) | ORR 14% |
| Relapsed After ASCT | |
| (Nagle et al, 2013) | Median OS 8 mos |

Abbreviations: ASCT, autologous stem cell transplant; mos, months; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; SD, stable disease.

These consistently discouraging results demonstrate that new treatment options are urgently needed for patients whose tumors have demonstrated a lack of response to chemotherapy.

This trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

## 2.2. Primary Mediastinal B-cell Lymphoma and Transformed Follicular Lymphoma

PMBCL has distinct clinical, pathological, and molecular characteristics compared to DLBCL. PMBCL is thought to arise from thymic (medullary) B cells and represents approximately 3% of patients diagnosed with large B-cell lymphoma. PMBCL is typically identified in the younger adult population in the fourth decade of life with a slight female predominance (Sehn et al, 1998; Savage et al, 2006). Gene expression profiling suggests deregulated pathways in PMBCL overlap with Hodgkin lymphoma. Initial therapy of PMBCL generally includes anthracycline-containing regimens with rituximab with or without involved field radiotherapy. A recent Phase 2, prospective study of infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab (DA-EPOCH-R) demonstrated radiotherapy may not be required (Dunleavy et al, 2013).

Follicular lymphoma (FL), a B cell lymphoma, is the most common indolent (slow-growing) form of NHL, accounting for approximately 20% to 30% of all NHLs. Some patients with FL will transform (TFL) histologically to DLBCL which is more aggressive and associated with a poor outcome. Histological transformation to DLBCL occurs at an annual rate of approximately 3% for 15 years with the risk of transformation continuing to drop in subsequent years. The biologic mechanism of histologic transformation is unknown. Initial treatment of TFL is influenced by prior therapies for follicular lymphoma but generally includes anthracycline-containing regimens with rituximab to eliminate the aggressive component of the disease (National Comprehensive Cancer Network 2014).

Treatment options for relapsed/refractory PMBCL and TFL are similar to those in DLBCL. Given the low prevalence of these diseases, no large prospective randomized studies in these patient populations have been conducted. Patients with chemotherapy refractory disease have a similar or worse prognosis (Kuruvilla et al, 2008) to those with refractory DLBCL.

In addition, the international, multicohort retrospective non-Hodgkin lymphoma research (SCHOLAR-1) study retrospectively evaluated outcomes in patients with chemorefractory DLBCL, PMBCL, and TFL. SCHOLAR-1 integrated data from two Phase 3 studies (LYSARC-CORAL and Canadian Cancer Trials Group LY.12) and 2 observational cohorts (MD Anderson Cancer Center and Mayo Clinic/University of Iowa Specialized Program of Research Excellence). Among 861 patients, 635 were included based on chemorefractory search criteria. Outcomes were consistently poor, regardless of refractory subgroup and across cohorts. The results of SCHOLAR-1 indicated that patients with chemorefractory, aggressive DLBCL represent a homogenous patient population with a response rate of 26% (complete response [CR] rate of 7%) and median overall survival of 6.3 months (Crump et al, 2017).

### 2.3. High Grade B-cell Lymphoma

In 2016, the World Health Organization introduced a new category of large B-cell lymphomas called high-grade B-cell lymphoma (HGBCL) (Swerdlow et al, 2016). This designation includes large B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements that are phenotypically intermediate to DLBCL or B-cell lymphoma, unclassifiable (this latter category has since been eliminated). MYC rearrangements in large B-cell lymphomas are associated with a poor prognosis that is worsened in cases of concomitant BCL2 and/or BCL6 alterations, ie, double- or triple-hit lymphomas. As such, patients with HGBCL are likely to face poor survival outcomes.

In summary, axicabtagene ciloleucel may provide a viable treatment option to relapsed/refractory large B-cell lymphoma patients with no other curative alternatives.

### 2.4. Study Rationale

As most advanced cancers eventually become refractory to conventional therapies, new treatment modalities are needed. Immunotherapy, which is based on the enhancement of an immune response against the tumor, is a promising approach to treating many cancer types. T cells play an important role in destroying diseased cells throughout the body. Studies with immune checkpoint inhibitors and tumor infiltrating lymphocytes have demonstrated the

potential of T cells to treat cancer. T cells need to possess the appropriate specificity for a tumor, be present in sufficient numbers, and overcome any local immunosuppressive factors to be effective. Engineered T cells are a promising approach for cancer therapy (Kershaw et al, 2013).

Engineered **a**utologous **c**ell **t**herapy (eACT™) is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target antigens expressed on the cell surface of specific malignancies (Kochenderfer et al, 2013). The ability to genetically engineer human T cells and use them to mediate cancer regression in patients has been demonstrated in a number of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B cell malignancies expressing the CD19 antigen.

### 2.4.1. CD19 and Expression

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

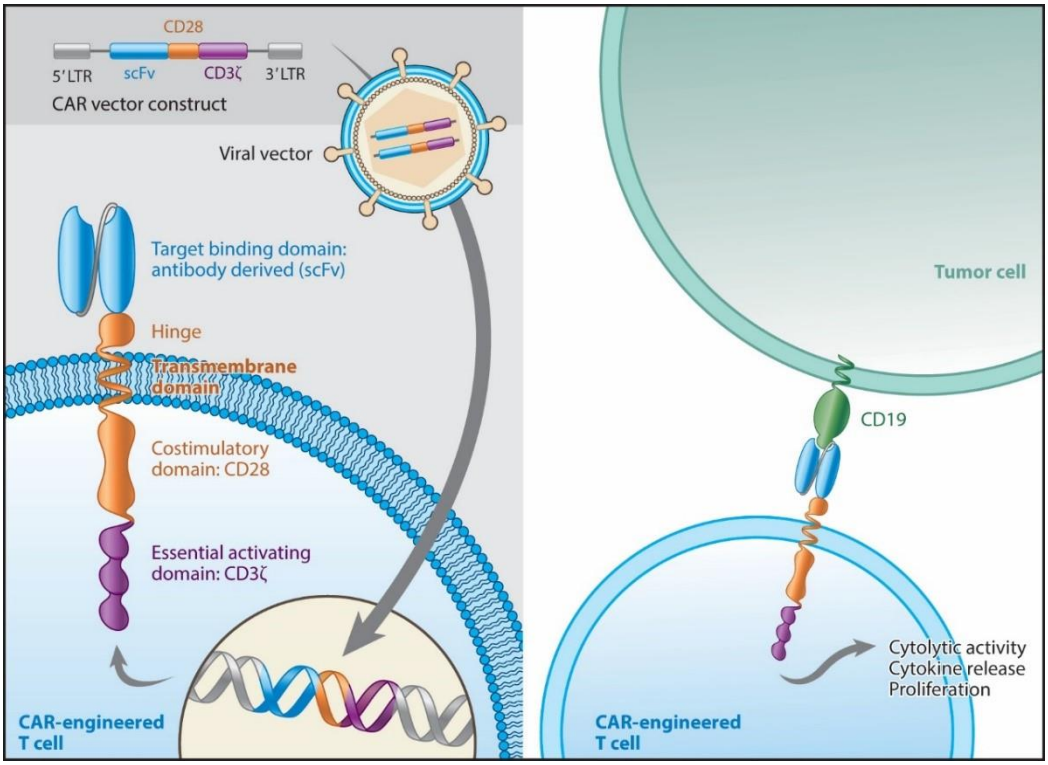
### 2.4.2. Anti-CD19 CAR T-cell Product

Anti-CD19 CAR T cells are autologous human T cells that have been engineered to express an extracellular single-chain variable fragment (scFv) with specificity for CD19 linked to an intracellular signaling part comprised of signaling domains from CD28 and CD3ζ (CD3-zeta) molecules arranged in tandem.

An anti-CD19 CAR vector construct has been designed, optimized and initially tested at the Surgery Branch of the National Cancer Institute (NCI, IND 13871) (Figure 2) (Kochenderfer et al, 2009; Kochenderfer et al, 2010). The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 (Nicholson et al, 1997). A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and persistence of anti-CD19 CAR T cells (Kowolik et al, 2006). The signaling domain of the CD3-zeta chain is essential for T cell activation. These fragments were cloned into the murine stem cell virus-based (MSGV1) vector, utilized to genetically engineer the autologous T cells. Treatment with anti-CD19 CAR T cells is currently being administered to subjects with CD19+ B cell malignancies in ongoing NCI protocol (09-C-0082; IND 13871). The same CAR vector construct will be used in this study.

The CAR construct is inserted into the T cells' genome by retroviral vector transduction. Briefly, peripheral blood mononuclear cells (PBMCs) are obtained by leukapheresis and Ficoll separation. Peripheral blood mononuclear cells are activated by culturing with an anti-CD3 antibody in the presence of recombinant interleukin 2 (IL-2). Stimulated cells are transduced with a retroviral vector containing an anti-CD19 CAR gene and propagated in culture to generate sufficient engineered T cells for administration.

**Figure 2. Axicabtagene Ciloleucel**




### 2.4.3. Prior Experience with Axicabtagene Ciloleucel and other Anti-CD19 CAR T Cells

Refer to the current axicabtagene ciloleucel Investigator's Brochure (IB) for the most current anti-CD19 CAR T-cell study results.

### 2.4.4. Axicabtagene Ciloleucel

Kite Pharma, Inc., (hereafter referred to as Kite Pharma or Kite) is developing an eACT™ (axicabtagene ciloleucel) that targets CD19 expression on B cell malignancies. The CAR vector construct is identical to the one used in NCI protocols (Surgery Branch protocol 09-C-0082; IND 13871; Pediatric Branch protocol 12-C-0112G; IND 14985). Kite Pharma in conjunction with the NCI Surgery Branch has developed a rapid, closed, and bead-less process for the generation of the anti-CD19 CAR T cells. Closing the process retains the characteristics of the T cell product (Better et al, 2014). See the investigational product manual for more details.

# 3. STUDY DESIGN

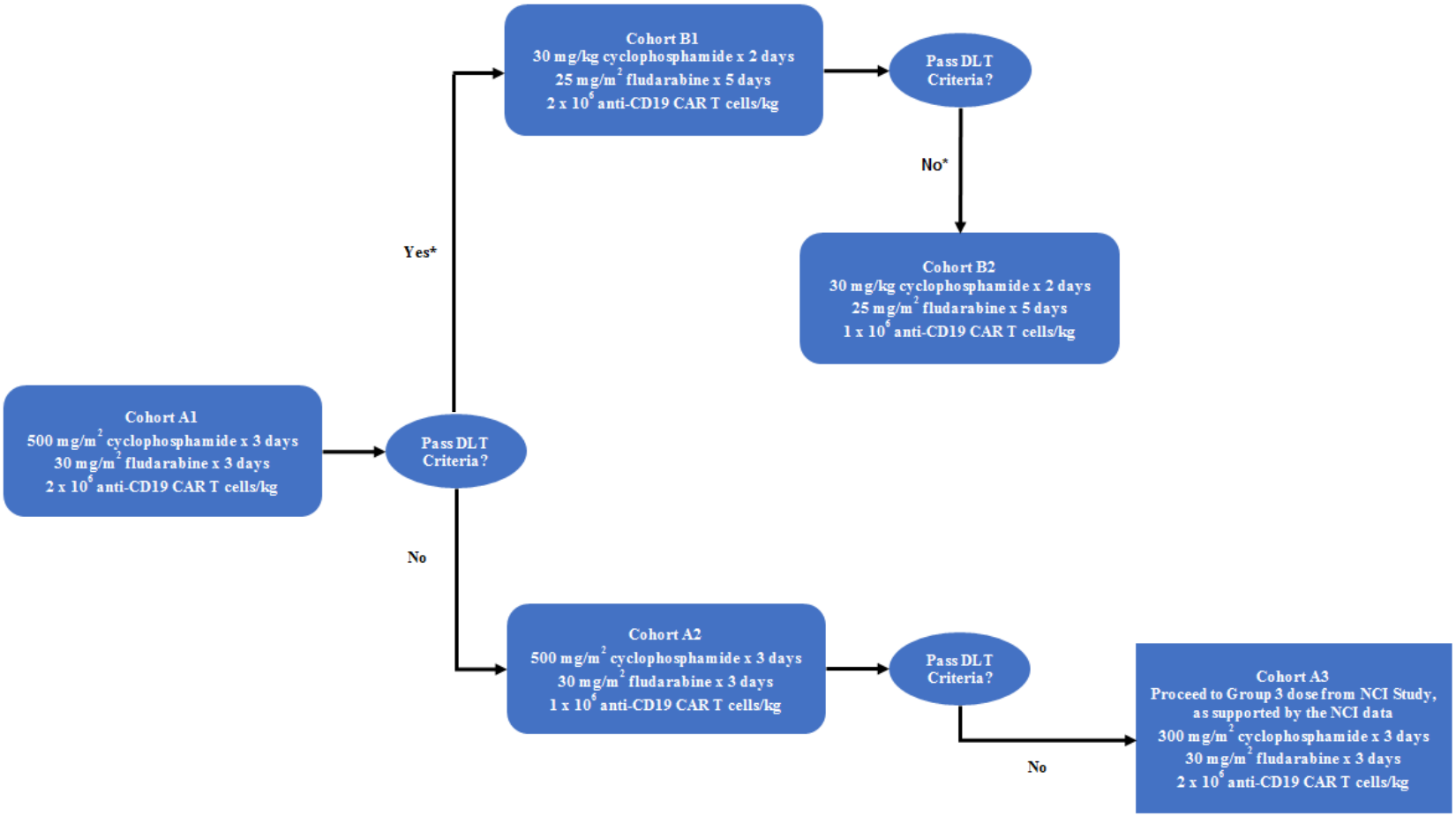
## 3.1. General Study Design

Study KTE-C19-101 is a Phase 1-2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory NHL. Study KTE-C19-101 will be separated into 3 distinct phases designated as Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (Cohort 3,Cohort 4, Cohort 5, **and Cohort 6**).

Phase 1 Study

During Phase 1, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or axicabtagene ciloleucel may be explored. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 3 and outlined in Section 9.10.

**Figure 3. Phase 1 Dosing Cohorts and Regimens**




*May be explored: see Section 9.6

Phase 2 Pivotal Study

In Phase 2 pivotal study, subjects will enroll into 2 separate cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL.
- TFL is defined as subjects who received prior chemotherapy for follicular lymphoma.

During the Phase 2 pivotal study, an independent data safety monitoring board (DSMB) will meet when 20 and 50 subjects in the modified intent-to-treat (mITT) set of Cohort 1 have had the opportunity to complete the 3 month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

Phase 2 Safety Management Study (SMS)

In the Phase 2 safety management study (SMS), subjects will enroll into **4** separate cohorts designated as Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**.

- Cohort 3 will enroll adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, or TFL.
- Cohort 4 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.
- Cohort 5 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.
- **Cohort 6 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy**.

The DSMB will meet to review safety data when 20 subjects in each Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. The DSMB may meet more often as needed.

Independent of the phase of the study each subject will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Bridging therapy (if applicable, for Phase 2 SMS) or debulking therapy (if applicable, Phase 2 SMS, Cohort 5)

- Conditioning chemotherapy period
- Investigational product (IP) treatment period
- Post treatment assessment period
- Long-term follow-up period

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

A study schema is drawn out and described at the end of the protocol synopsis section.

### 3.2. Participating Sites

Approximately 35 centers located in North America and Europe will participate in this study. During the conduct of the study, additional regions, countries or sites may be added as necessary.

### 3.3. Number of Subjects

Participants in this trial will be referred to as "subjects". It is anticipated that approximately **268** to **286** subjects will be enrolled and dosed in this study as defined below:

Phase 1 study: approximately 6 to 24 subjects

Phase 2 pivotal study: approximately 92 subjects enrolled into 2 cohorts

- Cohort 1: approximately 72 subjects
- Cohort 2: approximately 20 subjects

Phase 2 safety management study: approximately **170** subjects enrolled and dosed within **4** cohorts

- Cohort 3: approximately 40 subjects
- Cohort 4: approximately 40 subjects
- Cohort 5: approximately 50 subjects
- **Cohort 6: approximately 40 subjects**

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

## 3.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects are attained in the dose-limiting toxicity (DLT) evaluable (Phase 1) and mITT sets (Phase 2). Subjects who have not received the target dose of axicabtagene ciloleucel will be retained in the analyses of disposition and safety, where appropriate (Section 10.5).

## 3.5. Study Duration

### 3.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long term follow-up period, the duration of the study will take approximately 15 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment and survival.

The need for prolonged follow-up is based on the potential persistence of gene transfer vectors in treated subjects.

### 3.5.2. Completion of the Phase 2 Pivotal Study

Completion of the study is defined as the time at which the last subject completes the long-term follow-up period visit, is considered lost to follow-up, withdraws consent, or dies. The primary analyses will be conducted when 72 subjects in the mITT set of the Phase 2 pivotal Cohort 1 and 20 subjects in the mITT set of Cohort 2 have completed the 6 month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first.

# 4. SUBJECT SCREENING AND ENROLLMENT

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

Each subject who enters the screening period, which starts when the subject signs the informed consent form (ICF), will receive a unique subject identification (ID) number before any study specific procedures or activities are initiated. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject. Furthermore, the subject identification number must remain constant throughout the entire clinical study, it must not be changed after enrollment or if the subject is rescreened or retreated.

# 5. SUBJECT ELIGIBILITY

## 5.1. Inclusion Criteria

101) Histologically confirmed aggressive B cell NHL, including the following types defined by WHO 2008 (Campo et al, 2011):

- DLBCL not otherwise specified; T cell/histiocyte rich large B cell lymphoma; DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly;

  or

  — primary mediastinal (thymic) large B cell lymphoma

  — transformation of follicular lymphoma to DLBCL will also be included

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

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

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

  — Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy

  or

- No response to second or greater lines of therapy

  — PD as best response to most recent therapy regimen

  — 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

- Refractory post-ASCT

  — Disease progression or relapsed ≤ 12 months of ASCT (must have biopsy proven recurrence in relapsed subjects)

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

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

a) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and

b) an anthracycline containing chemotherapy regimen;

c) for subjects with transformed FL must have chemorefractory disease after transformation to DLBCL

104) At least 1 measurable lesion according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson et al, 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy

105) Magnetic resonance imaging (MRI) of the brain showing no evidence of central nervous system (CNS) 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, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time the subject is planned for leukapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).

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) ≥ 1000/uL

111) Platelet count ≥ 75,000/uL

112) Absolute lymphocyte count ≥ 100/uL

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%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings

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 postmenopausal for at least 2 years are not considered to be of childbearing potential)

Additional criteria specific for Phase 2 safety management study **(**Cohorts 3, 4, 5 **and 6)**:

115) Relapsed or refractory large B-cell lymphoma including DLBCL, PMBCL, TFL, and HGBCL after two systemic lines of therapy

### 5.2. Exclusion Criteria

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

202) History of Richter's transformation of CLL

203) Autologous stem cell transplant with therapeutic intent within 6 weeks of planned axicabtagene ciloleucel infusion

204) History of allogeneic stem cell transplantation

205) Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for re-treatment

206) Prior chimeric antigen receptor therapy or other genetically modified T cell therapy

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

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

209) 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.

210) Presence of any indwelling line or drain (e.g., 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

211) Subjects with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases

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

213) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

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

215) Expected or possible requirement for urgent therapy within 6 weeks due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome)

216) Primary immunodeficiency

217) History of symptomatic deep vein thrombosis or pulmonary embolism **requiring systemic anticoagulation** within 6 months of enrollment

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

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

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

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

222) Subjects of both genders who are not willing to practice birth control from the time of consent through 6 months after the completion of conditioning chemotherapy

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

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

# 6. PROTOCOL TREATMENT

## 6.1. Treatment Terminology

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

- Bridging therapy refers to treatment used to control a subject's disease prior to conditioning chemotherapy
- Debulking therapy refers to treatment used to reduce a subject's disease prior to conditioning chemotherapy
- The conditioning chemotherapy regimen used for this study will be fludarabine and cyclophosphamide.
- The investigational product for this study is named axicabtagene ciloleucel.
- The term study treatment refers to all protocol required therapies.

## 6.2. Study Treatment

### 6.2.1. Bridging Therapy for Phase 2 Safety Management Study, Cohort 3 (retreatment), Cohort 4, and Cohort 6

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.

At the discretion of the investigator, bridging therapy may be considered for subjects retreated in Cohort 3 or enrolled in Cohort 4 **and Cohort 6** with high disease burden at screening or baseline assessments (eg, bulky disease or rapidly progressing disease). Allowed bridging therapy regimens are outlined in Table 2. **Other bridging regimens may be considered but need to be discussed with the medical monitor on a case-by-case basis.**

**Table 2. 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.**<br><br>**Choice of corticosteroid and dose can be adjusted for age/comorbidities or per local or institutional guidelines** | **May be administered after apheresis/enrollment and must be completed prior to the start of conditioning chemotherapy**<br><br>***Note:*** **Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed therapy.** |
| **HDMP + Rituximab (Castro et al, 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 and completed at least 7 days prior to the start of conditioning chemotherapy**<br><br>***Note:*** **Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed.** |
| **Combination Chemotherapy (Vacirca et al, 2014) (Ohmachi et al, 2013)** | **B-R: Bendamustine (90 mg/m$^2$, Day 1+2); Rituximab (375 mg/m$^2$, Day 1)** | **May be administered after enrollment and completed at least 14 days prior to the start of conditioning chemotherapy, and subjects must remain eligible per the eligibility criteria outlined in Section 5 prior to the start of conditioning chemotherapy**<br><br>***Note:*** **Chemistry panel and CBC with differential must be repeated prior to start of conditioning chemotherapy to confirm eligibility to proceed.** |

**Abbreviations: IV, intravenous; CBC, complete blood count.**
a. The bridging therapy regimen may be chosen at the discretion of the investigator

### 6.2.2. Debulking Therapy for Phase 2 Safety Management Study, Cohort 5

Subjects enrolled into the Phase 2 Safety Management Study, Cohort 5 should receive debulking therapy to reduce lymphoma burden. Debulking therapy options are outlined in Table 3. Other debulking treatment options may be considered in select cases and must be discussed with the Kite medical monitor. The goal of the debulking therapy should be to optimally reduce lymphoma burden.

**Table 3. Debulking Therapy Regimens**

| Type | Proposed Regimen[a] | Timing/Washout |
|---|---|---|
| **R-CHOP** (Feugier et al, 2005) | **Rituximab 375 mg/m$^2$ Day 1**<br>**Doxorubicin 50 mg/m$^2$ Day 1**<br>**Prednisone 100 mg Day 1 through Day 5**<br>**Cyclophosphamide 750 mg/m$^2$ Day 1**<br>**Vincristine 1.4 mg/m$^2$ Day 1** | **Should be administered after leukapheresis/enrollment and should be completed at least 14 days prior to the start of conditioning chemotherapy** |
| **R-ICE** (Gisselbrecht et al, 2010) | **Rituximab 375 mg/m$^2$ Day 1**<br>**Ifosfamide 5 g/m2 24h-CI Day 2**<br>**Carboplatin AUC5 Day 2 maximum dose 800 mg**<br>**Etoposide 100 mg/m$^2$ /d Days 1 through Day 3** | |
| **R-GEMOX** (Mounier et al, 2013) | **Rituximab 375 mg/m$^2$ Day 1**<br>**Gemcitabine 1000 mg/m$^2$ Day 2**<br>**Oxaliplatin 100 mg/m$^2$ Day 2** | |
| **R-GDP** (Crump et al, 2004) (Gopal et al, 2010) | **Rituximab 375 mg/m$^2$ Day 1 (or Day 8)**<br>**Gemcitabine 1 g/m$^2$ on Day 1 and Day 8**<br>**Dexamethasone 40 mg on Day 1 through Day 4**<br>**Cisplatin 75 mg/m$^2$ on Day 1 (or carboplatin AUC5 on Day 1)** | |
| **Radiotherapy[b]** | **Per local standard up to 20 to 30 Gy** | **Should be administered after leukapheresis/enrollment and should be completed at least 5 days prior to the start of conditioning chemotherapy** |

Abbreviations: AUC, area under the curve.

a Other debulking treatment options may be used, but must be discussed with the medical monitor. Supportive care with hydration, anti-emesis, mesna, growth factor support, and tumor lysis prophylaxis according to local standard may be used. More than 1 cycle allowed.

b At least 1 target lesion should remain outside of the radiation field to allow for tumor measurements

### 6.2.3. Conditioning Chemotherapy

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.

#### 6.2.3.1. Fludarabine

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

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

#### 6.2.3.2. Cyclophosphamide

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

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

#### 6.2.3.3. 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.

### 6.2.4. Axicabtagene Ciloleucel

Refer to the most current IB regarding axicabtagene ciloleucel and clinical experience. This section contains general information and is not intended to provide specific instructions. Refer to the investigational product manual for details and instruction on storage and administration.

Axicabtagene ciloleucel is supplied cryopreserved in cryostorage bags. The product in the bag is slightly cloudy, with cream to yellow color. The cryostorage bags containing axicabtagene ciloleucel arrive frozen in a liquid nitrogen dry shipper. The bags must be stored in vapor phase of liquid nitrogen and the product remains frozen until the subject is ready for treatment to assure viable live autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

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

To date, subjects have received doses of anti-CD19 CAR T cells ranging from 1-30 x $10^6$ anti-CD19 CAR T cells/kg. There have been no instances of accidental overdose of subjects in this program. In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity.

If any problems related to the use of axicabtagene ciloleucel or any products that support the management of axicabtagene ciloleucel (eg, cryostorage bags, subject identification labels) required in this study are identified, please log on to www.kitepharma.com to report the complaint.

### 6.2.5. Concomitant Therapy

During the course of the study, investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care except those medications listed in Section 6.2.6.

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

For subjects who are enrolled but not dosed with axicabtagene ciloleucel, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study specific procedure (e.g., leukapheresis, conditioning chemotherapy). For subjects who are not enrolled (e.g., screen failure or not leukapheresed), only concurrent therapies related to any serious adverse event(s) will be recorded.

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

### 6.2.6. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis, and 5 days prior to axicabtagene ciloleucel administration. **For the prophylactic use of steroid for Cohort 6, refer to Section 7.13.7.**

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after axicabtagene ciloleucel administration, unless used to manage axicabtagene ciloleucel related toxicities (refer to the most current version of the IB). Other medications that might interfere with the evaluation of the investigational product, such as non-steroidal anti-inflammatory agents should also be avoided for the same time period unless medically necessary.

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

If permissibility of a specific medication/treatment is in question, please contact the Kite Pharma Medical Monitor.

### 6.2.7. Subsequent Therapy

Subsequent therapy administered after the 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, will be recorded until the subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies. For subjects who are enrolled, but do not receive axicabtagene ciloleucel infusion, any additional anti-cancer therapy will also be collected until the subject completes the long-term follow-up period, is considered lost to follow up, withdraws consent, or dies.

## 6.3. Study Treatment Schedule

### 6.3.1. Leukapheresis (Within Approximately 5 Days of Eligibility Confirmation)

Subjects will undergo leukapheresis to obtain leukocytes (white blood cells) for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the cell processing facility (CPF) overnight as described in the Investigational Product Manual**.** Once a subject commences leukapheresis, the subject is considered enrolled in the study.

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

Upon arrival at the CPF, each subject's leukapheresed product will be processed to enrich for the T cells containing PBMC fraction. T cells are then stimulated to expand and transduced with a retroviral vector to introduce the CAR gene. The T cells are then expanded and cryopreserved to generate the investigational product per CPF standard operating procedures (SOPs). Once the product has passed certain release tests, it will be shipped back to the treating facility. Following completion of each subject's conditioning chemotherapy regimen, subjects will receive their respective axicabtagene ciloleucel infusion.

### 6.3.2. Study Treatment

#### 6.3.2.1. Chemotherapy General Instructions

Subjects will receive a non-myeloablative conditioning regimen consisting of cyclophosphamide and fludarabine in order to induce lymphocyte depletion and create an optimal environment for expansion of axicabtagene ciloleucel *in vivo*. Subjects will initiate conditioning chemotherapy with cyclophosphamide and fludarabine beginning on Day -5 (or Day -7 for Cohort B) through Day -1. The 5-day conditioning chemotherapy regimen may be administered in an outpatient setting. The 7-day conditioning chemotherapy regimen may be administered as an outpatient or inpatient regimen per investigator's discretion.

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

For subjects enrolled into the Phase 2 Safety Management Study, Cohort 5 **and Cohort 6:**

Subjects who have not recovered their white blood cell (WBC) count by the time conditioning chemotherapy is scheduled to start, may skip the conditioning chemotherapy if the WBC is ≤ 1000/µL at this time. This option must be discussed with the Kite medical monitor.

#### 6.3.2.2. Axicabtagene Ciloleucel General Instructions

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

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

If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel-related non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (e.g., 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 neurologic toxicities > Grade 1, or if deemed necessary by the investigator.

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

- Acetaminophen 500 to 1000 mg PO
- Diphenhydramine (12.5 to 25 mg IV or 25 mg PO)

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 Investigational Product Manual. The Investigational Product Manual must be reviewed prior to administration of axicabtagene ciloleucel.

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

### 6.3.3. Rationale for Study Treatment Dosing

#### 6.3.3.1. Rationale for Conditioning Chemotherapy Dose in Phase 1 Cohort A1

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

As described in the IB**,** the NCI study (09-C-0082; IND 13871) evaluated three groups of subjects based on conditioning regimens. Group 3 evaluated cyclophosphamide (300 mg/m$^2$) and fludarabine (30 mg/m$^2$), both given for 3 concurrent days followed by 1-2 x $10^6$ anti-CD19 CAR T cells. Eleven subjects were treated with this regimen.

The DLT definition in the KTE-C19-101 study was applied to the NCI study (09-C-0082; IND 13871) data in group 3. There were no DLTs. The subject incidences of Grade 3, 4, 5, and serious adverse events attributed to CAR+ T-cells were 3 (27%), 0 (0%), 0 (0%), and 1 (9%). The ORR in this cohort was 60%, including 10% complete responses. Many subjects, however, did not achieve blood lymphocyte counts of zero with this conditioning regimen.

To improve the depth and duration of lymphocyte depletion, the conditioning chemotherapy dose in Phase 1 Cohort A1 will be cyclophosphamide (500 mg/m$^2$) and fludarabine (30 mg/m$^2$) both given for 3 concurrent days with the target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg. This regimen is currently being evaluated in the NCI study (09-C-0082; IND 13871). Cyclophosphamide (500 mg/m$^2$) and fludarabine (30 mg/m$^2$) both given for 3 concurrent days

has been studied and tolerated in subjects with B cell malignancies (O'Brien et al, 2001). Similar total doses of cyclophosphamide (900 to 2,000 mg/m$^2$) and fludarabine (90 to 150 mg/m$^2$) have been given as a reduced non-myeloblative conditioning regimen in subjects with B cell malignancies receiving allogeneic stem cell transplants (Khouri et al, 1998). The cyclophosphamide dose used in this regimen (Cohort A1 and currently in the NCI study 09-C-0082; IND 1387) is approximately 38% lower than that used in the Group 2 cyclophosphamide 30 mg/kg conditioning regimen from the NCI study (incidence of DLT 29%), with the same lower dose of fludarabine dose as Group 3. Evaluation of higher conditioning chemotherapy doses and/or varying anti-CD19 CAR T cell doses would proceed based on the incidence of DLT and evaluation of benefit-risk.

#### 6.3.3.2. Rationale for Conditioning Chemotherapy Dose in Phase 1 Cohort B1

Fifteen subjects were treated in the NCI protocol (09-C-0082; IND 13871) in group 2. Group 2 included subjects with leukemia and lymphoma, 2 different doses of cyclophosphamide (cumulative 60 and 120 mg/kg), and a range of CAR T cell doses (1-5 x $10^6$/kg). The DLT definition in the KTE-C19-101 study was applied to the NCI study data for subjects in group 2 with B-cell lymphomas, dosed at $\leq$ 2.5 x $10^6$ anti-CD19 CAR T cells, and 60 mg/kg cumulative dose of cyclophosphamide to reflect the KTE-C19-101 protocol. Seven subjects met these DLT criteria.

The subject incidence of DLT was 29%. Subject 1010014, with a best objective response of CR, had specific DLTs of Grade 3 renal insufficiency and hypoxia and Grade 4 hypotension and somnolence requiring intubation. Subject 1010021, with a best objective response of CR, had a specific DLT of Grade 3 motor neuropathy. All events were reversible. The subject incidence of Grade 3, 4, 5, and serious adverse events attributed to CAR T cells were 1 (14%), 2 (29%), 0 (0%), and 2 (29%). The Grade 4 events were Grade 4 hypotension, Grade 4 somnolence, and Grade 4 aphasia/dysphasia (3 events in 2 subjects) (data on file, Kite Pharma). The subject incidence ORR in this cohort was 6 (86%), including 5 (71%) complete responses of which 4 are ongoing.

The duration and depth of lymphodepletion appeared to be improved with this higher dose of cyclophosphamide conditioning chemotherapy (data on file, Kite Pharma). While the sample sizes are small, the data suggest that greater objective and complete response rates may be attained with a higher dose of conditioning chemotherapy regimen. Therefore, the regimen in Cohort B1 may be explored if the incidence of DLT in Cohort A1 is acceptable to further evaluate the impact of conditioning chemotherapy on benefit/risk.

**Table 4. Incidence of DLT and Response among Subjects with B-cell Lymphomas and Dosed with Group 2 and Group 3 Conditioning Chemotherapy and ≤ 2.5 x $10^6$ anti-CD19 CAR T Cells**

| Group | N | Incidence of DLT[a] – n(%) | ORR - n(%) | CR Rate – n(%) |
|---|---|---|---|---|
| Group 2 Conditioning (30 mg/kg Cy x 2 days, 25 mg/m$^2$ Flu x 5 days) | 7 | 2 (29) | 6 (86) | 5 (71) |
| Group 3 conditioning (300 mg/m$^2$ Cy x 3 days, 30 mg/m$^2$ Flu x 3 days) | 10[b] | 0 (0) | 6 (60) | 1 (10) |

a. DLT as determined by the definition proposed in the KTE-C19-101 study
b. 11 subjects treated in Group 3; 10 were followed through Day 30 at data cutoff

**Table 5. DLT[a] Events among Subjects with B-cell Lymphomas and Dosed with ≤ 1-2.0 x $10^6$ anti-CD19 CAR T Cells and Cyclosphosphamide 30 mg/kg x 2 Days-Fludarabine 25 mg/m$^2$ x 5 Days**

| Subject | Event |
|---|---|
| 1010014 | Grade 3 renal insufficiency, duration 9 days<br>Grade 4 hypotension, duration 3 days<br>Grade 3 hypoxia, duration 18 days<br>Grade 4 somnolence, duration 10 days, intubation required |
| 1010021 | Grade 3 motor neuropathy, duration 18 days |

a. DLT as determined by the definition proposed in the KTE-C19-101 study

#### 6.3.3.3. Rationale for Patient Population to be Included in Phase 2 Pivotal Study Cohort 1 and Cohort 2

In the multicenter randomized Phase 3 CORAL study where subjects were randomized to R-ICE or R-DHAP second-line therapy followed by ASCT with or without rituximab maintenance, 203 subjects across both arms did not proceed with ASCT. These subjects were ineligible for ASCT for multiple reasons including chemorefractory disease, early relapsed disease, residual masses after salvage therapy and intolerance to therapy. The median overall survival of these 203 ASCT ineligible subjects after salvage chemotherapy was only 4.4 months (Van Den Neste et al, 2016). Therefore, the efficacy of axicabtagene ciloleucel will be estimated in this population which represents a significant unmet need for more effective therapies.

#### 6.3.3.4. Rationale for Including Phase 2 Safety Management Study Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**

##### 6.3.3.4.1. Cohort 3

CRS and neurologic toxicities are two identified risks associated with axicabtagene ciloleucel. Both CRS and neurologic toxicities have led to Grade 4 or Grade 5 events in the context of anti-CD19 CAR T cells (Schuster et al, 2015; Turtle et al, 2016). The pathophysiology of CRS

is well described, but the etiology of the neurologic toxicities remains unclear. Currently it is hypothesized that there are two potential mechanisms of the pathophysiology of neurologic toxicities: 1) peripheral systemic cytokine release followed by cytokine diffusion across the blood brain barrier (BBB) and/or 2) peripherally activated anti-CD19 CAR T cells translocate across the BBB and elicits a local inflammatory effect. The later hypothesis is supported by emerging evidence of CAR T-cells trafficking to the CSF. To further elucidate the pathophysiology of neurologic toxicities, serial CSF collections will be analyzed in this study for cytokines/chemokines/effector molecules and anti-CD19 CAR T cells. In addition, in an attempt to mitigate the onset and severity of CRS and neurologic toxicities, prophylactic tocilizumab and levetiracetam will be administered in Cohort 3 (see Section 6.3.4). It is hypothesized that tocilizumab may lead to fewer activated CAR T-cells trafficking to the CNS and levetiracetam may reduce the risk of clinical or subclinical seizures. Lastly, in an effort to mitigate the severity and/or duration of the neurologic toxicities, IT-Ara C with corticosteroids is recommended to be administered at the onset of Grade 3 neurologic toxicities (see Section 6.4.1).

#### 6.3.3.4.2. Cohort 4 **and Cohort 6**

In the Phase 2 pivotal study portion of ZUMA-1 (n = 101), CAR T-cell levels were associated with response (P = 0.0002), with a 5.4-fold higher area under the curve (AUC) within the first 28 days post-treatment for responders versus non-responders. However, CAR T-cell levels and specific cytokines, including IL-2, GM-CSF, and ferritin, were only associated with Grade 3 or higher neurologic toxicity suggesting that distinct mechanisms may underlie the pathogenesis of these adverse events, as shown in Figure 4 and (Locke et al, 2017). While there is a theoretical concern for the use of immunosuppressive agents to manage CRS or neurologic toxicities, tocilizumab and/or corticosteroids usage did not appear to affect negatively the overall response in ZUMA-1 and CAR T-cell levels (Table 6). Prophylactic tocilizumab use in Cohort 3 appeared to lower the rate of Grade 3 or higher CRS but not neurologic toxicities (Table 7). To further refine the use of corticosteroids to treat CRS and neurologic toxicities, Cohort 4 **and Cohort 6** will **recommend** corticosteroids at lower toxicity grades to determine the impact on incidence and severity of CRS and neurologic toxicities (Section 6.4.1). **Cohort 6 will further build on this rationale by initiating corticosteroids as prophylactic treatment on Day 0, Day 1, and Day 2**. Prophylactic tocilizumab will not be used in Cohort 4, **Cohort 5, or Cohort 6** (Section 6.3.4).

**Figure 4** **Axicabtagene Ciloleucel Expansion and Correlations with Response and Adverse Events**

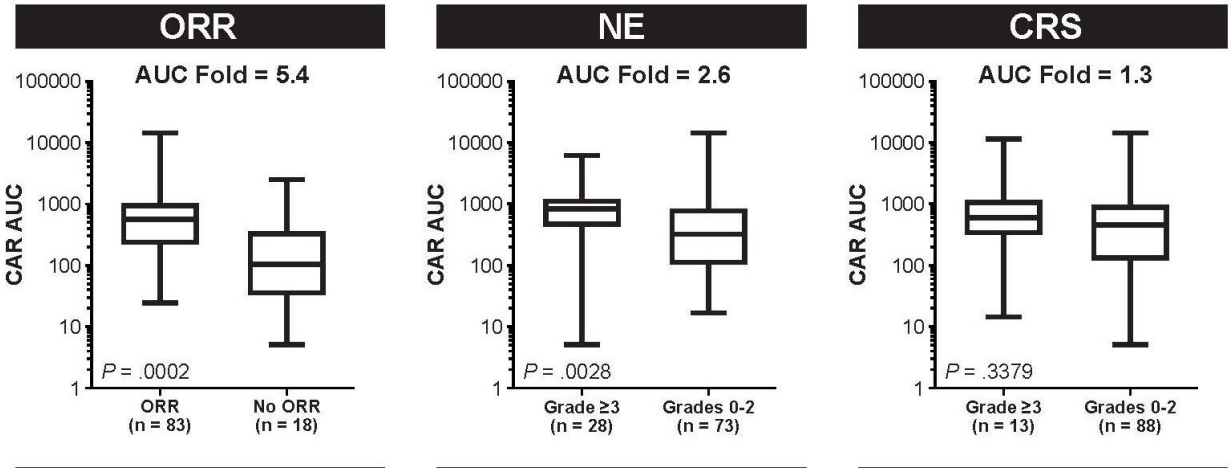



**Table 6.** **Tocilizumab and Corticosteroids Use in ZUMA-1 Phase 2 Pivotal Study Primary Analysis**

| | No Tocilizumab n = 58 | Tocilizumab n = 43 | *P* Value | No corticosteroids n = 74 | Corticosteroids n = 27 | P Value |
|---|---|---|---|---|---|---|
| ORR, n (%) | 47 (81.0) | 36 (83.7) | .8 | 62 (83.8) | 21 (77.8) | .56 |
| CR, n (%) | 33 (56.9) | 22 (51.2) | .69 | 40 (54.1) | 15 (55.6) | 1 |
| Ongoing, n (%) | 28 (48.3) | 16 (37.2) | .31 | 33 (44.6) | 11 (40.7) | .82 |
| Median peak CAR levels, cells/µL (range) | 26.52 (1.25-1226.36) | 61.06 (0.84-1513.69) | .0011 | 32.2 (1.25-1226.36) | 49.69 (0.84-1513.69) | .0618 |
| Median CAR AUC, cells/µL days (range) | 289.49 (16.82-14329.29) | 743.85 (5.09-11506.59) | .0022 | 407.53 (16.82-14329.29) | 724.98 (5.09-11506.59) | .0967 |

(Neelapu et al, 2017)

**Table 7. Rates of Neurologic Toxicities and CRS in the Phase 1 and 2 Pivotal Study versus Phase 2 Safety Management Study Cohort 3**

| | ZUMA-1 Phase 1+ Phase 2 Pivotal Cohorts 1+2 (N = 108) | ZUMA-1 SMS Cohort 3 (N = 34) |
|---|---|---|
| Any Neurologic toxicity[a] | 70 (65) | 29 (85) |
| Worst Grade 1 | 23 (21) | 9 (26) |
| Worst Grade 2 | 15 (14) | 6 (18) |
| Worst Grade 3 | **29 (27)** | **12 (35)** |
| Worst Grade 4 | **3 (3)** | **1 (3)** |
| Worst Grade 5 | **0 (0)** | **1 (3)** |
| due to disease progression | **0 (0)** | **0 (0)** |
| Worst Grade >= 3 | **32 (30)** | **14 (41)** |
| Any CRS[b] | 101(94) | 32 (94) |
| Worst Grade 1 | 41 (38) | 12 (35) |
| Worst Grade 2 | 45 (42) | 19 (56) |
| Worst Grade 3 | **9 (8)** | **0 (0)** |
| Worst Grade 4 | **4 (4)** | **1 (3)** |
| Worst Grade 5 | **1 (1)** | **0 (0)** |
| due to disease progression | **0 (0)** | **0 (0)** |
| Worst Grade >= 3 | **14 (13)** | **1 (3)** |

Data cut for Phase 1, Phase 2 Cohort 1 and 2: Primary Analysis, DCO 27JAN2017.
Data cut of SMS Cohort 3: Updated Analysis, DCO 11AUG2017.
Neurologic events are graded per CTCAE 4.03; CRS events are graded per Lee grade (Lee et al, 2014).

a. Neurologic AEs were identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy (Topp et al, 2015). For Phase 1, Phase 2 Cohort 1 and 2, the neurologic toxicities included events with onset between date of first axicabtagene ciloleucel infusion (Day 0) and Day 56; for SMS Cohort 3, the neurologic toxicities included events with onset on or after the date of first conditioning chemotherapy.
b. One subject in Phase 1 had CRS symptoms reported but not graded for CRS at the time at the Primary Analysis data cut. This subject was counted in the "Any CRS" row but not by the worst grade.

#### 6.3.3.4.3. Cohort 5

In the pivotal cohorts of ZUMA-1, Phase 2 (Cohorts 1 and 2; n = 101), subjects with relapsed and refractory aggressive B-cell lymphoma were not permitted to receive anti-cancer therapy between leukapheresis and conditioning chemotherapy. However, a subsequent retrospective analysis suggested a relationship between lymphoma burden (estimated by the sum of the product of diameters [SPD] of index lesions) and clinical outcomes (Locke et al, 2018). Subjects with the lowest SPD had the highest rates of ongoing response at 1 year and the lowest rates of CRS and neurological events. Thus, Cohort 5 will be used to prospectively assess the impact of debulking therapy, administered after leukapheresis but prior to conditioning chemotherapy, on

the safety and efficacy of axicabtagene ciloleucel. The goal of the debulking therapy will be to reduce lymphoma burden and assess clinical outcomes.

Furthermore, the majority (90%) of patients with relapsed/refractory (r/r) DLBCL who were included in another CAR T-cell therapy study (KYMRIAH™ and Novartis Pharmaceuticals Corporation 2018) received the investigator's choice of bridging therapy that may have had a debulking effect. Although debulking was not explicitly tested, 8 of these patients had no measurable disease following bridging therapy. The overall results from this study suggested that the inclusion of the investigator's choice of bridging therapy was well-tolerated, as no new safety signals were identified using this approach. Toxicities observed within the JULIET study were consistent with other CD19-targeted CAR T-cell therapies.

In conclusion, the goal of Cohort 5 is to improve the benefit-risk ratio of axicabtagene ciloleucel by reducing lymphoma burden prior to administration of axicabtagene ciloleucel. This approach is justified by a retrospective analysis of outcome by tumor burden in ZUMA-1 and data from other CD19-targeting CAR T-cell products. The specific safety regimens studied in Cohorts 3 and 4 will not be continued in Cohort 5.

### 6.3.4. Study Treatment by Phase

Phase 1 Study

The study will begin with Cohort A1. Subsequent cohorts may be explored as depicted in Figure 3 and outlined in Section 9.10.

Conditioning Chemotherapy

Cohorts A1/A2: Subjects will receive the following 5-day chemotherapy regimen:

- IV hydration with 1 L of 0.9% sodium chloride (NaCl) given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500 mg/m$^2$ IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30 mg/m$^2$ IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1 L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

Cohort A3: Subjects will receive the following 5-day chemotherapy regimen:

- The IV hydration is 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 300 mg/m$^2$ IV over 60 minutes on Day -5, Day -4, and Day -3 followed by:

- Fludarabine 30 mg/m$^2$ IV over 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1 L of 0.9% NaCl at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

For subjects enrolled into Cohort A1/A2/A3, Day -2 and Day -1 will be rest days before axicabtagene ciloleucel infusion on Day 0.

Cohorts B1/B2: Subjects will receive the following 7 day chemotherapy regimen:

- IV hydration with 0.9% NaCl. Recommended at 2.6 ml/kg/hr (maximum 200ml/hr) administered as a continuous infusion starting 11 hours pre-cyclophosphamide infusion and continue hydration until 24 hours after last cyclophosphamide infusion:
- Cyclophosphamide 30 mg/kg IV administered on Day -7 and Day -6 infused over 120 minutes followed by:
- Fludarabine 25 mg/m$^2$ IV administered on Day -5, Day -4, Day -3, Day -2 and Day -1. Each infusion given over 30 minutes
- Add mesna per institutional guidelines

For subjects enrolled into Cohort B1/B2, there will be no rest days between the last day of chemotherapy (Day -1) and the axicabtagene ciloleucel infusion on Day 0.

#### 6.3.4.1.1. Axicabtagene Ciloleucel

Cohorts A1/A3/B1: Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg (± 20%; 1.6 x $10^6$ anti-CD19 CAR T cells/kg to 2.4 x $10^6$ anti-CD19 CAR T cells/kg). A minimum dose of 1 x $10^6$ anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x $10^8$ anti-CD19 CAR T cells will be administered.

Cohorts A2/B2: Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 1 x $10^6$ anti-CD19 CAR T cells/kg (± 20%; 0.8 x $10^6$ anti-CD19 CAR T cells/kg to 1.2 x $10^6$ anti-CD19 CAR T cells/kg). A minimum dose of 0.5 x $10^6$ anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of either 1 x $10^8$ anti-CD19 CAR T cells will be administered.

6.3.4.2. Phase 2 Pivotal Study:

Based on the safety profile of the 6 DLT evaluable subjects from the Phase 1 portion of the study, the SRT deemed the axicabtagene ciloleucel dosing regimen explored in Cohort A1 to be safe.

In Phase 2, subjects will receive the 5-day conditioning chemotherapy regimen used in Cohort A1 of the Phase 1 portion of the study:

- IV hydration with 1 L of 0.9% NaCl (or isotonic [crystalloid] fluid) given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500 mg/m$^2$ IV over approximately 60 minutes on Day -5, Day -4, and Day -3 followed by:
- Fludarabine 30 mg/m$^2$ IV over approximately 30 minutes on Day -5, Day -4, and Day -3 followed by:
- An additional 1 L of 0.9% NaCl (or isotonic [crystalloid] fluid) at the completion of the fludarabine infusion
- Add mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines

Axicabtagene ciloleucel will be administered at a target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg. In addition, subjects who receive doses between 1-2 x $10^6$ anti-CD19 CAR T cells/kg will be included in the mITT analysis set. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x $10^8$ anti-CD19 CAR T cells will be administered.

Phase 2 Safety Management Study:

For Cohort 3, subjects will receive conditioning chemotherapy and axicabtagene ciloleucel as described above. In addition, subjects will receive levetiracetam (750 mg PO or IV BID) starting on Day 0. At the onset of ≥ Grade 2 neurologic toxicities, levetiracetam should be administered. If a subject does not experience any ≥ Grade 2 neurologic toxicities, levetiracetam should be tapered and discontinued as clinically indicated. Subjects will also receive tocilizumab (8 mg/kg IV over 1 hour [not to exceed 800 mg]) on Day 2. Further tocilizumab (± corticosteroids) is recommended to be administered at the onset of ≥ Grade 2 CRS.

For Cohort**s** 4 **and 6**, subjects will receive bridging therapy (if applicable, refer to Section 6.2.1), conditioning chemotherapy, axicabtagene ciloleucel, and levetiracetam, as described above. Tocilizumab will not be administered as prophylaxis, but **will be administered** based on toxicity management guidance (eg, tocilizumab and corticosteroids) as described in Section 6.4.1, Table 8, Table 9, and Table 10. Corticosteroids will be initiated for toxicity management for Grade 2 CRS and for Grade 1 neurologic toxicities per Table 8 and Table 9, respectively, as described in Section 6.4.1. **In addition, in Cohort 6, subjects will receive corticosteroids on Day 0 (pre-infusion), Day 1, and Day 2**.

For Cohort 5, subjects should receive debulking therapy (refer to Section 6.2.2), conditioning chemotherapy, axicabtagene ciloleucel, and levetiracetam, as described above. Toxicity management guidance is provided in Section 6.4.

## 6.4. Toxicity Management

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

As the safety experience with axicabtagene ciloleucel increases, the management guidance may be updated. Therefore, it is important 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.

### 6.4.1. Phase 2 Safety Management Study (Cohort 4 and Cohort 6 only)

**To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, hypogammaglobulinemia, and cytopenias. For CRS and neurological toxicities,** the treatment guidance outlined in Table 8, Table 9, and Table 10 will be used for Cohort 4 **and Cohort 6** of the Phase 2 safety management study. Additional safety information and management recommendations **for the other identified risks** can also be found in the most current version of the IB.

**Table 8. Grading and Management of CRS in Cohort 4 and Cohort 6**

| CRS Grade | Supportive Care | Tocilizumab | Steroids | Follow up |
|---|---|---|---|---|
| **Grade 1:**<br>• Symptoms are not life threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise) | • Supportive care per institutional standard of care | N/A | N/A | **Not improving after 24 hours:**<br>• **Tocilizumab as per Grade 2 guidance (below)**<br>Not improving after 3 days:<br>• Dexamethasone 10 mg x1 |

| CRS Grade | Supportive Care | Tocilizumab | Steroids | Follow up |
|---|---|---|---|---|
| **Grade 2:**<br>• Symptoms require and respond to moderate intervention<br>• Oxygen requirement <40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor[a] or Grade 2 organ toxicity[b] | • Continuous cardiac telemetry and pulse oximetry as indicated<br>• IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids<br>• Vasopressor support for hypotension not responsive to IV fluids<br>• Supplemental oxygen as indicated | • Tocilizumab: 8mg/kg over 1 hour (not to exceed 800 mg)<br>• Repeat tocilizumab every 4 to 6 hours as needed if not response to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period.<br>• Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS | • Dexamethasone 10mg x 1 | Improving:<br>• Discontinue tocilizumab<br>• Taper corticosteroids<br>Not Improving:<br>• Manage as Grade 3 (below) |
| **Grade 3:**<br>• Symptoms require and respond to aggressive intervention<br>• Oxygen requirement ≥ 40% FiO2 or hypotension requiring high-dose or multiple vasopressors[a] or Grade 3 organ toxicity or Grade 4 transaminitis[b] | • Management in monitored care or intensive care unit | • Per Grade 2 | • Methylprednisolone 1 mg/kg IV BID[c] | Improving:<br>• Discontinue tocilizumab<br>• Taper corticosteroids<br>Not Improving:<br>• Manage as Grade 4 (below) |
| **Grade 4:**<br>• Life-threatening symptoms<br>• Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD)<br>• Grade 4 organ toxicity (excluding transaminitis)[b] | • Per Grade 3<br>• Mechanical ventilation and/or renal replacement therapy may be required | • Per Grade 2 | High-dose corticosteroids:<br>• Methylprednisolone 1000 mg/day IV x 3 d ays | Improving:<br>• Discontinue tocilizumab<br>• Taper corticosteroids<br>Not improving:<br>• Consider 1 gram BID to TID of methylprednisolone and other immunosuppressives (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess) |

a. High-dose vasopressor doses
b. Severity based on CTCAE
c. or equivalent dexamethasone

## Table 9. Grading and Management of Neurologic Toxicities in Cohort 4 and Cohort 6

| Neurologic Toxicities | Supportive Care | Tocilizumab | Corticosteroids | Follow up |
|---|---|---|---|---|
| **Grade 1 examples include:**<br>• Somnolence-mild drowsiness or sleepiness<br>• Confusion-mild disorientation<br>• Encephalopathy-mild limiting of ADLs<br>• Dysphagia-not impairing ability to communicate | • Supportive care per institutional standard of care<br>• Closely monitor neurologic status<br>• Consider prophylactic levetiracetam | N/A | • Dexamethasone 10mg x 1 | Not improving after 2 days:<br>• Repeat dexamethasone 10mg x 1<br>• Continue supportive care |
| **Grade 2 examples include:**<br>• Somnolence-moderate, limiting instrumental ADLs<br>• Confusion-moderate disorientation<br>• Encephalopathy-limiting instrumental ADLs<br>• Dysphagia-moderate impairing ability to communicate spontaneously<br>• Seizure(s) | • Continuous cardiac telemetry and pulse oximetry as indicated<br>• Closely monitor neurologic status with serial neuro exams to include fundoscopy and Glasgow Coma Score. Consider neurology consult<br>• Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications<br>• Levetiracetam/ antiepileptics if subject has seizures | • **Only** in case of concurrent CRS:<br>• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)<br>• Repeat tocilizumab every 4 to 6 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period.<br>Maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS | • Dexamethasone 10mg QID | Improving:<br>• Discontinue tocilizumab<br>• Taper corticosteroids<br>• Not improving:<br>• Manage as Grade 3 (below) |

| Neurologic Toxicities | Supportive Care | Tocilizumab | Corticosteroids | Follow up |
|---|---|---|---|---|
| **Grade 3 examples include:**<br>• Somnolence-obtundation or stupor<br>• Confusion-severe disorientation<br>• Encephalopathy-limiting self-care ADLs<br>• Dysphagia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly | • Management in monitored care of intensive care unit | • Per Grade 2 | • Methylprednisolone 1 gram daily | Improving:<br>• Discontinue tocilizumab<br>• Taper corticosteroids<br>• Not improving:<br>• Manage as Grade 4 (below) |
| **Grade 4 examples include:**<br>• Life-threatening consequences<br>• Urgent intervention indicated<br>• Requirement for mechanical ventilation<br>• Consider cerebral edema | • Per Grade 3<br>• Mechanical ventilation, may be required | • Per Grade 2 | • Methylprednisolone 1 gram BID | Improving:<br>• Taper corticosteroids<br>Not improving:<br>• Consider 1 gram of methylprednisolone TID, alternative immunsuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2mg/kg x 1 and reassess) |

**Table 10. Management of Cerebral Edema in Cohort 4 and Cohort 6**

| Supportive Care | Tocilizumab | Corticosteroids | Follow up |
|---|---|---|---|
| As above for neurologic toxicities Grade 4, to include:<br>• Intensive care unit supportive therapy<br>• Optimal head position with elevation of head of bed and straight neck positioning<br>• Administration of diuretics and osmotherapy (eg, mannitol, hypertonic saline)<br>• If cerebral edema documented strongly suspected, recommend neurosurgical consult<br>• Early tracheal intubation with controlled mechanical mild hyperventilation and good oxygenation<br>• Maintain cerebral perfusion pressure with mild hypervolemia<br>• Avoid hypertension with use of antihypertensives (labetalol, nicardipine)<br>• Avoid potent vasodilators<br>• Pharmacological cerebral metabolic suppression (barbiturates, sedation, analgesia, and neuromuscular paralysis, as indicated)<br>  • Maintain rigorous glycemic control | • Tocilizumab as above in Grade 4 neurologic toxicity management (tocilizumab should be given only if concurrent CRS) | • Methylprednisone 1gram BID | Improving:<br>• Very slow steroid taper recommended;<br>• Repeat neuro-imaging as indicated<br>• Serial neurologic exams as indicated<br>• Consider early neuro-rehabilitation<br>• Discontinue tocilizumab if started<br>Not Improving<br>• Consider Methylprednisolone 1gram TID, alternative immunosuppressive (e.g. siltuximab) and anti-thymocyte globulin (ATG 2 mg/kg x1 and reassess) |

### 6.4.2. Phase 2 Safety Management Study (Cohort 5)

To date, the following risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, hypogammaglobulinemia and cytopenias. Please refer to the current version of the IB for details and management.

# 7. STUDY PROCEDURES

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

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in Section 7. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

## 7.1. Informed Consent

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits and the potential risks. Subjects should sign the most current IRB/IEC approved ICF prior to any study specific activity or procedure is performed.

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

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

## 7.2. Demographic Data

Demographic data will be collected to include sex, age, race, ethnicity**,** and country of enrollment to study their possible association with subject safety and treatment effectiveness.

## 7.3. Medical and Treatment History

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

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

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

## 7.4. Physical Exam, Vital Signs, Performance Status, and EQ-5D

Physical exams will be performed during screening and at times noted in the SOA. Changes noted in subsequent exams when compared to the baseline exam will be reported as an adverse event.

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

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

For subjects enrolled in Cohort 3, Cohort 4, **Cohort 5 or, Cohort 6**, EQ-5D will be completed by the subject, prior to any other assessment, at the screening visit and at other times noted in the SOA. Subjects who are blind or illiterate may have the EQ-5D questions read to them by the study staff. The study staff, however, cannot interpret any of the questions for the subject. A subject may be exempt from completing the questionnaire if he or she is unable to read the questionnaire in one of the country languages available.

The EQ-5D is a 2 page generic patient questionnaire for assessing the overall health status of a subject. The EQ-5D consists of a 5 dimension descriptive system including questions on mobility, self-care, usual activities, pain/comfort, and anxiety/depression and a visual analogue scale (EQ VAS) which allows the respondent to record health on a vertical scale (eg, best health to worst health) thus allowing a quantitative measure of health outcome.

### 7.5. Neurological Assessment

For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessments will be standardized by using the Mini-Mental State Examination (MMSE) standard version 2.0. The MMSE neurological assessment will not be required for Phase 2 SMS Cohort 4, **Cohort** 5**, and Cohort 6**. The MMSE is a 5-10 minute, 11-question measure that examines various areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands.

The MMSE is divided into two sections. The first part requires vocal responses to the examiner's questions. In the second part of the exam, the subject is asked to follow verbal and written instructions, write a sentence spontaneously, and copy a geometric figure**.** Every attempt should be made to dedicate a single research staff member trained in the administration of the MMSE to conduct the assessment to minimize variability among different assessors.

A full neurological assessment will be completed during screening to establish a baseline. Subsequent assessments will be performed before axicabtagene ciloleucel administration on Day 0, on Day 1, and then every other day during the 7-day post-infusion monitoring period, as well as at the Week 4 and Month 3 visits.

### 7.6. Cardiac Function

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

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

### 7.7. Magnetic Resonance Imaging

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

Evaluation of any new onset of ≥ Grade 2 neurologic toxicities should include a brain MRI as described in Section 6.4.

### 7.8. Bone Marrow Biopsy

Bone marrow aspirate/biopsy will be performed at screening if not previously performed to assess bone marrow involvement. For subjects with a potential complete response to axicabtagene ciloleucel, a follow-up bone marrow aspirate/biopsy will be performed in subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. To confirm a complete response, the bone marrow aspirate and biopsy must show no evidence of disease by morphology or if indeterminate by morphology it must be negative by immunohistochemistry. Refer to Section 7.10 and Appendix Afor treatment response assessment requirements per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007). Bone marrow aspirate/biopsy should also be considered to evaluate hemophagocytic lymphohistiocytosis (HLH) as indicated in the IB. A portion of the bone marrow sample collected to evaluate HLH or other toxicities should be submitted to the central laboratory as outlined in the central laboratory manual.

### 7.9. Lumbar Puncture

Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture performed at the screening visit for examination of cerebral spinal fluid. In addition, lumbar puncture may be performed as applicable for subjects with new onset of ≥ Grade 2 neurologic toxicities after axicabtagene ciloleucel infusion (see Section 6.4).

For subjects who sign the optional portion of the consent form, on study paired lumbar puncture for collection of CSF samples will be performed at baseline prior to axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion per the schedule of assessments. Samples

will be submitted to the central laboratory and analyzed for changes in cytokine levels and presence of CAR T cells.

Phase 2 Safety Management Study

For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **or Cohort 6**, lumbar punctures for the collection of CSF samples will be performed pre- and post-axicabtagene ciloleucel infusion at times outlined in the SOA. Samples will be submitted to the central laboratory as outlined in the central laboratory manual. Adequate platelet support should be provided prior to performing a lumbar puncture (e.g. platelet >50,000/$mm^3$).

### 7.10. Disease Response Assessment

Subjects will be evaluated for disease response by the site investigator at times indicated in the SOA. Disease assessments will be evaluated per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007). Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

Baseline positron emission tomography-computed tomography (PET-CT) scans of the neck, chest, abdomen and pelvis, along with the appropriate imaging of all other sites of disease are required. Subjects will undergo additional PET-CT tumor assessments after their axicabtagene ciloleucel infusion. The first of these post-treatment PET-CT tumor assessments will occur 4 weeks after infusion; subsequent assessments will occur at regular intervals throughout the post-treatment and long-term follow-up portions of the study, as highlighted in the SOA.

After axicabtagene ciloleucel administration, disease assessments will be used to determine the time when progressive disease occurs. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA.

A bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR. Per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007), a bone marrow aspirate and biopsy should be performed only when the subject had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. 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 to assign a CR to treatment.

In addition to the investigator's assessment, PET-CT scans of all subjects evaluated for disease response for Phase 2 pivotal study (Cohort 1 and Cohort 2) will be submitted to and reviewed by an independent central reviewer. For subjects who discontinue the study due to an assessment of progressive disease which was not subsequently confirmed by a central radiology reviewer, any additional imaging data, subsequent to the image in question will be submitted to the central reviewer to confirm disease response.

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

Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

### 7.11. Laboratory

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

Local lab analysis:

- Sodium (Na), potassium (K), chloride (Cl), total $CO_2$ (bicarbonate), creatinine, glucose, blood urea nitrogen (BUN) or urea (if BUN test cannot be analyzed by the local lab), albumin, calcium total, magnesium total (Mg), inorganic phosphorus, alkaline phosphatase, ALT/glutamic-pyruvic transaminase (GPT), AST/glutamic-oxaloacetic transaminase (GOT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), uric acid

- C-reactive protein (CRP)

- Complete blood count (CBC) with differential

- A urine or serum sample will be collected and assessed locally for females of childbearing potential. If the screening pregnancy test is positive, the subjects should not be enrolled. If a standard of care pregnancy test is collected during the course of the study, and the result is positive, the investigator should contact the Kite Pharma medical monitor for instructions. If a female partner of a male subject becomes pregnant during the conduct of the study, it must be reported by contacting Kite Pharma Medical Monitor for instructions.

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

Central lab analysis:

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

- Serum samples will also be evaluated centrally for anti-axicabtagene ciloleucel antibodies.

- For serum samples that demonstrate increased anti-axicabtagene ciloleucel antibodies at the Month 3 visit over baseline values, attempts should be made to obtain and test additional serum samples approximately every 3 months until the antibody levels return to baseline (or becomes negative) or up to 1 year from the completion of treatment, whichever occurs first.

- Archived tumor tissue

- For subjects enrolled in Cohort 4, Cohort 5, **and Cohort 6**, a block or 30 unstained slides should be submitted to the central laboratory for confirmatory diagnosis, CD19 expression, cell of origin, and determination of double/triple hit high grade lymphoma.

- For subjects who sign the optional portion of the informed consent, fresh tumor samples will be collected for central pathology review and evaluation of prognostic markers specific for large B-cell lymphoma and pertaining to the tumor immune environment. Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA (somatic mutations), RNA, or protein markers.

- CSF and possibly bone marrow samples will also be collected and analyzed at the central laboratory as outlined in the schedule of assessments and per Section 7.12.

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

## 7.12. Biomarkers

Biomarker analysis will be performed on blood and tumor samples to evaluate pharmacodynamic markers for axicabtagene ciloleucel. Prognostic markers specific for large B-cell lymphoma and related to the tumor immune environment may also be evaluated in archived and fresh tumor biopsies.

The presence, expansion, persistence, and immunophenotype of transduced anti-CD19 CAR T cells will be monitored in the blood primarily by polymerase chain reaction (PCR) analysis, complemented by flow cytometry. Expansion and persistence in peripheral blood will also be monitored by a CD19 CAR specific quantitative polymerase chain reaction (qPCR) assay.

Levels of serum cytokines will be evaluated in serum to characterize the pharmacodynamic and safety profile of axicabtagene ciloleucel. The following pro-inflammatory, homeostatic and immune modulating cytokines may be included in the panel: IL-6, IL-15, IL-17a, TNF-α, GM-CSF, IFN-γ, IL-12p40/p70 and IL-13; immune effector molecules: Granzyme A, B and Perforin; correlates of acute phase response: CRP and SAA; Chemokines MIP-1α, MIP-1β, MCP-1, IP-10, and IL-8. In addition, IL1Ra, IL2Rα, and ferritin will also be measured.

CSF, as well as additional samples (eg, pleural fluid), may be harvested from subjects who develop neurologic toxicities or CRS to enable evaluation of inflammatory cytokines and chemokine levels. 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.

Phase 2 Pivotal Study

For subjects in Cohort 1 and Cohort 2 who sign the optional portion of the consent form, on-study paired lumbar puncture for collection of CSF samples will be performed at baseline

prior to axicabtagene ciloleucel infusion and after axicabtagene ciloleucel infusion per the schedule of assessments. Samples will be analyzed for changes in cytokine levels and presence of CAR T cells.

Phase 2 Safety Management Study

For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **or Cohort 6,** lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, after axicabtagene ciloleucel infusion on Day 5 (± 3 days), and at the Week 4 visit (± 3 days). Collection of CSF samples will enable measurement of baseline cytokine levels prior to axicabtagene ciloleucel infusion. Changes in levels of cytokines after axicabtagene ciloleucel infusion will be measured at the time of peak CAR T-cell expansion (Day 5) and at Week 4 when it is anticipated that cytokine levels would return to baseline levels. Infiltration of CAR T cells will also be assessed by flow cytometry in post-axicabtagene ciloleucel infusion CSF samples. Exploratory analysis of cells, analytes, or immune cell markers within the CSF will be analyzed in conjunction with the clinical data to better understand the pathogenesis of neurologic toxicities.

For subjects enrolled in Cohort 4, Cohort 5, **and Cohort 6**, additional blood will be collected on **Day 1 (Cohort 6 only), Day 2 (Cohort 6 only),** Day 3, Day 7, Day 10, and Week 3 after axicabtagene ciloleucel infusion. The intent of the additional blood samples is to enable early monitoring of anti-CD19 CAR T-cell and serum cytokine levels in the blood of subjects treated more aggressively with tocilizumab and corticosteroids. To balance the total amount of blood drawn over the first 3 months of therapy, blood volumes have been reduced at pre-specified time points (refer to the central laboratory manual for details).

Phase 2 Pivotal Study and Safety Management Study

Bone marrow samples may be collected for subjects who develop toxicities after axicabtagene ciloleucel infusion and will be analyzed centrally by immunohistochemistry for evidence of disease, treatment emergent toxicities (e.g. HLH, pancytopenia) and presence of anti-CD19 CAR T cells.

Because axicabtagene ciloleucel comprises retroviral vector transduced T cells, the presence of RCR in the blood of treated subjects will be monitored.

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

Archived tumor tissue will be collected for central **pathology** review. Additional analysis may include CD19 expression, gene expression profiling, and analysis of DNA alterations. Remaining tumor samples may be stored for future exploratory analysis of DNA, RNA, or protein markers.

For subjects who sign the optional portion of the consent form (and for all subjects with accessible tumor), on-study paired core biopsies of tumor will be performed at baseline and after axicabtagene ciloleucel infusion when we expect expansion and tumor infiltration with CAR T cells. In addition, persisting, relapsing or emerging lesions could also be biopsied to help determine eligibility for re-treatment or mechanisms of tumor resistance. Exploratory analysis of tumor or immune cell markers that correlate with response to axicabtagene ciloleucel or disease prognosis will be analyzed.

The above samples and any other components from these samples may be stored up to 15 years to address exploratory research scientific questions related to the treatment or disease under study. Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who in turn can contact the sponsor. The investigator should provide the sponsor the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor and any data that may be generated will be entered in the study database.

## 7.13. Description of Study Periods

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

### 7.13.1. Screening

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

After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in Section 5 and who commence leukapheresis will be enrolled in the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening.

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

- Medical history and disease assessment
- Physical examination including height and weight

- Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.

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

- ECOG performance status

- For subjects enrolled in Cohort 3, Cohort 4, **Cohort 5, and Cohort 6**, EQ-5D questionnaire (prior to any other assessments/procedures being performed)

- For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessment including MMSE

- ECG

- ECHO for LVEF and pericardial effusion assessment

- An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility

- Imaging Studies

- Brain MRI

- Baseline PET-CT of the neck, chest, abdomen and pelvis

- PET-CT performed following the subjects last line of therapy and prior to signing the consent may be used for confirmation of eligibility**.**

- If PET CT is performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, the scans must be repeated to establish a new baseline. For subjects in Cohort 5, if no conditioning chemotherapy is being administered, a PET-CT must be repeated to establish a new baseline prior to the axicabtagene ciloleucel infusion**.** PET-CT should be performed as close to enrollment as possible.

- Bone marrow aspirate/biopsy as needed (if not done at initial diagnosis or between diagnosis and screening)

- Labs

- Chemistry panel

- CBC with differential

- β-HCG pregnancy test (serum or urine) on all women of child-bearing potential

- Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation and previous cancer treatment history
- Once eligibility confirmed, collection of archived tumor sample, as well as fresh tumor sample**(s)** and CSF samples (for subjects who signed the optional portion of the consent)
- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, lumbar puncture for collection of CSF samples to be performed after eligibility confirmed and prior to start of conditioning chemotherapy

### 7.13.2. Rescreening

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

### 7.13.3. Enrollment/Leukapheresis

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

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

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

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

The following procedures/requirements will occur on the leukapheresis collection day and as outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Weight
- Labs (to be drawn prior to leukapheresis, on the day of or day before leukapheresis)
- Chemistry panel
- CBC with differential
- CRP; if CRP is ≥ 100 mg/L a call must be made to the Kite medical monitor before proceeding with conditioning chemotherapy
- Anti-CD19 CAR T cells
- Lymphocyte subsets
- Cytokine levels
- Anti-axicabtagene ciloleucel antibodies
- Leukapheresis
- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

#### 7.13.4. Bridging Therapy Phase 2 Safety Management Study

If prescribed, bridging therapy must be administered after enrollment and completed prior to initiating conditioning chemotherapy per the specifications outlined in Section 6 for bridging therapy.

- Adverse/Serious Adverse Event reporting
- Concomitant medications documentation

#### 7.13.5. Debulking Therapy Phase 2 Safety Management Study, Cohort 5

Debulking chemotherapy must be administered after enrollment and should be completed at least 14 days prior to initiating conditioning chemotherapy or at least 14 days prior to axicabtagene ciloleucel administration in case conditioning chemotherapy is omitted. Radiotherapy must be administered after enrollment and should be completed at least 5 days prior to initiating conditioning chemotherapy or at least 5 days prior to axicabtagene ciloleucel administration in case conditioning chemotherapy is omitted.

### 7.13.6. Conditioning Chemotherapy Period

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

If PET-CT will be older than 28 days at the initiation of conditioning chemotherapy or if the subject receives any anti-cancer therapy with therapeutic intent (eg, radiation, supraphysiologic doses of steroids, chemotherapy) between the last PET-CT and initiation of conditioning chemotherapy, the PET-CT must be repeated to establish a new baseline.

Subjects in Cohort 5 **and Cohort 6** may proceed with conditioning chemotherapy in absence of measurable disease in the new baseline PET-CT **if they have received preceding bridging or debulking therapy (Cohort 5).**

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

#### 7.13.6.1. Requirements for Initiating Conditioning Chemotherapy

Administration of anti-CD19 CAR T cells to subjects with ongoing infection or inflammation, even if such processes are asymptomatic, increases the risk of high grade and fatal toxicity. All efforts should be made to rule out such conditions prior to cell infusion. Signs, symptoms or abnormal laboratory results attributed to the malignancy (eg "tumor fever," elevated CRP) are diagnoses of exclusion that require a documented workup to establish. Conditioning chemotherapy and axicabtagene ciloleucel infusion should only be initiated after it is reasonably assured that cell infusion can safely proceed.

If any of the following criteria are met prior to initiation of conditioning chemotherapy, then the work-up listed in Section 7.13.7.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°Celsius within **72** hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential that is suggestive of infectious process, and is observed between enrollment and the initiation 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, ears, eyes, nose, and throat (HEENT) exam, cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.

- The subject must not have received systemic antimicrobials for the treatment of known or suspected infection within 48 hours before 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 the subject is confirmed to have an infectious process for which antimicrobials are not available (eg, viral pneumonia), the infection must be clinically resolved as determined by the investigator and in consultation with infectious disease service (if applicable).

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

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

7.13.6.2. Conditioning Chemotherapy Administration

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

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

- Labs (to be drawn prior to chemotherapy)

- Chemistry Panel

- CBC with differential

- Fludarabine and cyclophosphamide administration

- Adverse/Serious Adverse Event reporting

- Concomitant medications documentation

- **Cytokine levels (Cohort 5 only)**

### 7.13.7. Investigational Product Treatment Period

7.13.7.1. Requirements for Initiating Axicabtagene Ciloleucel Infusion

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the work-up listed in Section 7.13.7.3 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°Celsius within **72** hours of axicabtagene ciloleucel infusion.
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- WBC count or WBC differential, that is suggestive of infectious process, and is observed between enrollment and the initiation of axicabtagene ciloleucel infusion (eg, WBC > 20,000/µL, rapidly increasing WBC, or differential with high percentage or segments/bands)
- Additionally: If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and 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 exam, 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**. For Cohort 6 only, dexamethasone 10 mg by mouth should be given prior to axicabtagene ciloleuclel infusion (refer to Section 7.13.7.2).**

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

#### 7.13.7.2. Monitoring After Axicabtagene Ciloleucel Infusion

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

If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel related non-hematological toxicities return 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 central neurologic toxicities > Grade 1, or if deemed necessary by the investigator.

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

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

- Neurological assessment including MMSE for subjects enrolled in Cohort 1, Cohort 2, or Cohort 3
- MMSE will be administered before treatment with axicabtagene ciloleucel on Day 0, and then on Day 1 and every other day during the 7-day post-infusion monitoring period.
- Vital signs including blood pressure, heart rate, oxygen saturation, and temperature, daily at a health care facility for at least 7 days
- Labs (before axicabtagene ciloleucel infusion, as described in the SOA)
- Chemistry Panel
- CBC with differential
- Lymphocyte subsets
- Cytokine levels

- Anti-CD19 CAR T cells
- RCR analysis
- **Cohort 6 only: Dexamethasone 10 mg by mouth on Day 0 (in the morning before the axicabtagene ciloleucel infusion), Day 1, and Day 2**
- Infusion of axicabtagene ciloleucel
- For subjects enrolled in Cohort 3, administer tocilizumab at a dose of 80 mg/kg IV over 1 hour (not to exceed 800 mg) on Day 2. See Section 6.3.4 for further details on additional tocilizumab administration for toxicity management.
- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, administer levetiracetam at a dose of 750 mg (PO or IV) BID starting on Day 0. See Section 6.4 for further details on administration and discontinuation of levetiracetam for toxicity management. If subject does not experience any neurologic toxicities ≥ Grade 2, taper and discontinue levetiracetam as clinically indicated.
- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, lumbar puncture for collection of CSF samples at Day 5 (± 3 days)
- Subjects in Cohort 5 **and Cohort 6** may proceed with axicabtagene ciloleucel if the new baseline PET-CT shows an absence of measurable disease**.**
- As applicable, lumbar puncture, for subjects with new onset Grade ≥ 2 neurologic symptoms after axicabtagene ciloleucel infusion or subjects who signed the optional portion of the consent, should be completed for examination of CSF.
- Collection of fresh tumor sample(s) for subjects who signed the optional portion of the consent (anytime between Day 7 and Day 14) Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)
- Concomitant medications documentation

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

#### 7.13.7.3. Requirements for 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 the following:

- 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 x 2 bottles each) and urinalysis and urine culture. Deep/induced sputum culture if clinically indicated.

  — All indwelling lines, such as central venous catheters, should be examined for any signs of infection and additional cultures should be drawn from the line

  — Nasopharyngeal-throat swab or equivalent assay for viral infection such as influenza A/B (including H1N1), parainfluenza 1/2/3, adenovirus, respiratory syncytial virus, coronavirus, metapneumovirus

  — Collection of fungal cultures and markers as appropriate (eg, galactomannan, fungitell)

  — Collection of appropriate serum viral studies (eg, cytomegalovirus [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 for repeat conditioning chemotherapy.

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

### 7.13.8. Post-treatment Assessment Period

After completing axicabtagene ciloleucel infusion and completing the minimum 7-day observation period, all subjects will be followed in the post-treatment assessment period. Counting from Day 0 (axicabtagene ciloleucel infusion), subjects will return to the clinic at the following intervals.

- Week 2 (± 2 days)

- Week 3 (± 2 days) for subjects enrolled in Cohort 4 only

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

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

- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- For subjects enrolled in Cohort 1, Cohort 2, or Cohort 3, neurological assessment including MMSE
- PET-CT for disease assessment: If the PET-CT is not of high enough resolution, the scan must be repeated. Refer to the imaging charter for detailed instructions.
- As applicable, bone marrow aspirate/biopsy to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment)
- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Labs
- Chemistry Panel
- CBC with differential
- β-HCG pregnancy test (serum or urine) on all women of child-bearing potential
- Anti-axicabtagene ciloleucel antibodies
- Cytokine levels
- Lymphocyte subsets
- Anti-CD19 CAR T cells
- RCR analysis

- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, taper or discontinue levetiracetam as clinically indicated. See Section 6.4 for further details.

- For subjects assigned to Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, lumbar puncture for collection of CSF samples at Week 4 (± 3 days)

- Adverse/Serious Adverse Event reporting (refer to Section 9 for safety reporting guidelines)

- Concomitant medications documentation

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

- PBMCs (anti-CD19 CAR T cells)

- Cytokines

At any time during the post treatment assessment period, if a subject progresses and is either not eligible for re-treatment or chooses not to pursue re-treatment, the subject will proceed directly to the Month 3 visit and be followed for survival, subsequent therapy and disease outcomes in the long term follow-up period. A PBMC (for anti-CD19 CAR T cells) and serum sample (for cytokine evaluation) should be collected at the time of progression, prior to starting any subsequent anti-cancer therapy.

Upon disease progression, sites are encouraged to collect a tumor biopsy and submit a portion of the tumor tissue to the central laboratory for exploratory biomarker analysis.

### 7.13.9. Long-term Follow-up Period

All enrolled subjects will be followed in the long term follow-up period for survival and disease status, if applicable. Subjects will begin the long term follow-up period after they have completed the Month 3 visit of the post treatment assessment period (whether they have responded to treatment or went straight to the Month 3 visit due to disease progression)

- Every 3 months (± 2 weeks) through Month 18

- Every 6 months (± 1 month) between Month 24 - Month 60

- Beginning with year 6, Month 72 (± 3 months), subjects will return to the clinic 1 time annually up to 15 years.

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

- For subjects enrolled in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, EQ-5D questionnaire (prior to any other assessments/procedures being performed)
- Physical exam
- PET-CT/ Disease assessment through 24 months or until disease progression, whichever occurs first. If subject's disease has not progressed by Month 24, disease assessments will continue to be performed per institutional standard of care.
- Survival status
- Labs
- CBC with differential
- Anti-axicabtagene ciloleucel antibodies (refer to Section 7.11)
- Lymphocyte subsets
- Anti-CD19 CART-cell **levels**
- RCR analysis
- Subsequent therapy for the treatment of NHL
- Refer to Sections 9.2 and 9.4 for targeted adverse/serious adverse event reporting
- Neurological, hematological, infections, autoimmune disorders, and secondary malignancies
- Targeted concomitant medication documentation (for 24 months or until disease progression, whichever occurs first)
- Gammaglobulins, immunosuppressive drugs, anti-infectives, and vaccinations

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

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

Upon disease progression, sites are encouraged to collect a tumor biopsy and submit a portion of the tumor tissue to the central laboratory for exploratory biomarker analysis.

The following procedures/assessments will be completed for subjects who are enrolled, but do not receive axicabtagene ciloleucel, at the time points outlined in the SOA:

- Subsequent therapy for the treatment of NHL
- Survival status
- Disease assessment per standard of care
- Adverse/Serious Adverse Event reporting and concomitant medication documentation until 30 days after last procedure (e.g., leukapheresis, conditioning chemotherapy).

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

### 7.13.10. Retreatment

Subjects who achieve a partial response (PR) or CR will have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel under the following conditions:

- Subject had a PR or CR
- Subjects disease subsequently progress
- CD19 tumor expression confirmed locally by biopsy after disease progression and prior to re-treatment. A portion of the biopsy should be sent to the central laboratory.
- Subject continues to meet the original study eligibility criteria with exception of prior axicabtagene ciloleucel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility.
- Subject has not received subsequent therapy for the treatment of lymphoma
- Subject did not experience a DLT in Phase 1 or a comparable toxicity in Phase 2
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to re-treatment
- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing antibody develops subject may be retreated if they meet the original study eligibility criteria)

The decision to administer re-treatment should be made in consultation with the Kite Medical Monitor. In addition, a discussion regarding benefits and risks of retreatment and including the potential need to undergo leukapheresis a second time for the manufacturing of axicabtagene

ciloleucel should occur with the subject prior to performing any study related procedures or treatment. This conversation should also be recorded in the subject's source document.

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

Subjects enrolled in Phase 2 will receive the same axicabtagene ciloleucel regimen **as** the original target dose. Subjects enrolled in Phase 1 will receive the axicabtagene ciloleucel regimen selected for Phase 2 if they are retreated. If the Phase 2 regimen has not yet been selected, subjects will receive the last axicabtagene ciloleucel regimen that was determined safe by the SRT.

Allowance for retreatment is based on clinical experience reported in the 2 studies conducted at the pediatric (Lee et al, 2015) and Surgery Branch (Kochenderfer et al, 2015) of the NCI where 6 subjects in total have been re-treated upon progression. Three of the re-treated subjects (indolent lymphoma/leukemia) experienced durable responses to retreatment after an initial response and disease progression.

## Table 11. Schedule of Assessments

| **Procedures** | **Screening** | **Enrollment/ Leukapheresis** | **Debulking Therapy (Cohort 5)** | **Conditioning Chemotherapy Period** | | | | | **IP Administration Period[12]** | | **Post Treatment Follow-up (each visit calculated from Day 0)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Within 28 days of enrollment | Within approx. 5 days of eligibility confirmation | **After enrollment and at least 14 days prior to Day -5** | -5 | -4 | -3 | -2 | -1 | 0 | 1 - 7 | Week 2 (± 2 days) | Week 3 (± 2 days) | Week 4 (± 3 days) | Month 2 (± 1 week) | Month 3 (± 1 week) |
| Medical history | X | | | | | | | | | | | | | | |
| ECOG Performance Status | X | | | | | | | | | | | | | | |
| EQ-5D Questionnaire (Cohort 3,4 and 5 only) | X | | | | | | | | | | | | X | | X |
| Neurological assessment including Mini Mental Status Exam (MMSE)[5] | X | | | | | | | | X | QOD [5] | | | X | | X |
| ECG | X | | | | | | | | | | | | | | |
| ECHO | X | | | | | | | | | | | | | | |
| Archival/Fresh tumor[1] | X | | | | | | | | | between Day 7 & Day 14 | | | | | |
| Brain MRI | X | | | | | | | | | | | | | | |
| PET-CT/ disease assessment [2] | X | | | | | | | | | | | | X | | X |
| Physical exam | X | | | | | | | | | | X | | X | X | X |
| Vital signs (BP, HR, $O_2$ sat, temp) | X | X | | X | X | X | | | X | X | X | | X | X | X |
| Weight **(**plus Height at screening**)** | X | X | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | X | | | | | | | | | | | | | | X |
| Lumbar Puncture[6] | X | | | | | | | | | X | | | X | | |
| Blood draw for Chemistry panel | X | X | | X | X | X | | | X | X | X | | X | X | X |
| Blood draw for CBC w/differential | X | X | | X | X | X | | | X | X | X | | X | X | X |
| Blood draw for C-reactive protein (CRP) | | X | | | | | | | | | | | | | |
| Blood draw for Anti-axicabtagene ciloleucel antibodies [3] | | X | | | | | | | | | | | X | | X |
| Blood draw for Lymphocyte subsets | | X | | | | | | | X | | | | X | | X |
| Blood draw for Cytokines [7, 11] | | X | | **X** [11] | | | | | X | QOD [11] | X | | X | | |

| **Procedures** | **Screening** | **Enrollment/ Leukapheresis** | **Debulking Therapy (Cohort 5)** | **Conditioning Chemotherapy Period** | | | | | **IP Administration Period[12]** | | **Post Treatment Follow-up (each visit calculated from Day 0)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Within 28 days of enrollment | Within approx. 5 days of eligibility confirmation | **After enrollment and at least 14 days prior to Day -5** | -5 | -4 | -3 | -2 | -1 | 0 | 1 - 7 | Week 2 (± 2 days) | Week 3 (± 2 days) | Week 4 (± 3 days) | Month 2 (± 1 week) | Month 3 (± 1 week) |
| Blood draw for Anti-CD19 CAR T cells[7, 10] | | X | | | | | | | X | Day **1[10],2[10],** 3, 7, 10 | X | X | X | | X |
| Blood draw for RCR analysis [4] | | | | | | | | | X | | | | | | X |
| Leukapheresis | | X | | | | | | | | | | | | | |
| Debulking Therapy **(Cohort 5 only)** | | | X | | | | | | | | | | | | |
| Fludarabine/Cyclophosphamide | | | | X | X | X | | | | | | | | | |
| **Prophylactic Steroid[13] (Cohort 6 only)** | | | | | | | | | **X[13]** | **X[13]** | | | | | |
| Axicabtagene ciloleucel infusion IV | | | | | | | | | X | | | | | | |
| Tocilizumab[8] | | | | | | | | | | Day 2 | | | | | |
| Levetiracetam[9] | | | | | | | | | Starting on Day 0 | | | | | | |
| Adverse events/ Concomitant medication | X | X | | → | | | | | | | | | | | |

1. Archival/Fresh tumor sample: Either FFPE tumor block or up to 20 unstained slides. For subjects enrolled in Cohort 4 Cohort 5, **and Cohort 6**, a block or 30 unstained slides. Fresh tumor sample for subjects who sign the optional portion of consent Archived and fresh tumor samples (if applicable) will be submitted to central laboratory after eligibility has been confirmed and prior to start of conditioning chemotherapy. Post treatment fresh tumor samples (if applicable) will be collected/submitted anytime between Day 7 and Day 14. See Section 7.11 and 7.12 and central laboratory manual for details
2. PET-CT (Neck-Chest-Abdomen-Pelvis)/disease assessment PET-CT performed following last line of therapy (>28 days from enrollment) may be used for confirmation of eligibility. If PET-CT performed > 28 days prior to the initiation of conditioning chemotherapy or if subject receives any anti-cancer therapy between screening and conditioning chemotherapy, baseline scans must be repeated. Screening PET-CT should be completed as close to enrollment as possible. As applicable, bone marrow aspirate/biopsy will be performed to confirm response (i.e., for subjects presenting with bone marrow involvement prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment). Bone marrow samples may also be collected and analyzed centrally for subjects who develop toxicities post axicabtagene ciloleucel. See Section 7.10 and Section 7.12
3. Blood draw for Anti-axicabtagene ciloleucel antibodies: Baseline antibody sample to be collected prior to start of leukapheresis. Post axicabtagene ciloleucel antibody sample to be collected at Week 4 and Month 3 visits. See Section 7.11 for further details
4. Blood draw for RCR: on Day 0 prior to administration of axicabtagene ciloleucel and at Month 3, 6 and 12; then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.
5. MMSE and Cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1 and then every other day during the 7 day post infusion monitoring period for Cohort 1, Cohort 2, and Cohort 3. MMSE will not be required for Cohort 4 **,** Cohort 5, **and Cohort 6.**
6. Lumbar Puncture: subjects with symptoms of CNS malignancy (e.g., new onset severe headaches, neck stiffness, or focal neurological findings) will have lumbar puncture performed at screening to assess cerebral spinal fluid for possible CNS involvement. Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumber puncture performed to assess cerebral spinal fluid. In addition, subjects who sign the optional portion of the consent, will have lumbar puncture for

the collection of CSF performed at baseline prior to axicabtagene ciloleucel infusion and post axicabtagene ciloleucel infusion (Day 5 ± 3 days). For subjects enrolled in Cohort 3,Cohort 4, Cohort 5, **and Cohort 6**, lumbar punctures for collection of CSF samples will be performed at the following time points: after eligibility is confirmed and prior to start of conditioning chemotherapy, post axicabtagene ciloleucel infusion on Day 5 (±3 days), and at the Week 4 visit (±3 days).

7. If a subject is admitted to the hospital within the 7-day observation period is discharged and then subsequently re-admitted to the hospital with any axicabtagene ciloleucel related adverse events, blood samples for anti-CD19 CAR T cells and cytokines will be collected on day of hospital re-admission and then weekly through and including the day of discharge. Blood samples for anti-CD19 CAR T cells and cytokines should also be collected at the time of disease progression prior to starting any subsequent anticancer therapy.
8. For subjects enrolled in Cohort 3, administer tocilizumab at a dose of 8 mg/kg IV over 1 hour (not to exceed 800mg) on Day 2. See Sections 6.3.4 for further details.
9. For subjects enrolled in Cohorts 3, 4**,** 5, **and 6**, administer levetiracetam at a dose of 750 mg (PO or IV) BID starting on Day 0. See Sections 6.3.4 and 6.4.1 for further details.
10. For subjects enrolled in Cohorts 4 and 5, blood draw for Anti-CD19 CAR T cells will be collected on Day 3, **Day 7**, Day 10. **For subjects enrolled in Cohort 6, blood draw for anti-CD19 CAR T cells will be collected on Day 1, Day 2, Day 3, Day 7, and Day 10.**
11. **Blood draw for** cytokines: prior to axicabtagene ciloleucel infusion on Day 0, then on Day 1, and then every other day during the 7 day post infusion monitoring period. **For subjects enrolled in Cohort 5, additional cytokine sample after debulking therapy from Day -5 prior to conditioning chemotherapy. For subjects enrolled in Cohort 6, additional cytokine sample will be drawn on Day 2.**
12. Refer to Appendix B for requirements by country regulatory agencies.
13. **For subjects enrolled in Cohort 6, administer dexamethasone 10 mg by mouth on Day 0 (prior to axicabtagene ciloleucel infusion), Day 1, and Day 2.**

## Table 12. Schedule of Assessments (Long-term Follow-up Period)

| **Procedure** | **Long Term Follow-up Period (Each visit calculated from Day 0)** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Frequency | Month 6 | Month 9 | Month 12 | Month 15 | Month 18 | Month 24 | Month 30 | Month 36 | Month 42 | Month 48 | Month 54 | Month 60 | Month 72 and Annually Thereafter |
| EQ-5D Questionnaire **(**Cohorts 3, 4, 5, **and 6 only)** | X | | | | | | | | | | | | |
| Physical exam[1] | X | X | X | X | X | X | | | | | | | |
| PET-CT/disease assessment[2] | X | X | X | X | X | X | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] |
| Survival Status | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood draw for CBC w/differential [3] | X | X | X | X | X | X | | | | | | | |
| Blood draw for Anti-axicabtagene ciloleucel antibodies [4] | X | X | X | | | | | | | | | | |
| Blood draw for Lymphocyte subsets [3] | X | X | X | X | X | X | | | | | | | |
| Blood draw for anti-CD19 CAR T cells[3] | X | | X | | | X | | | | | | | |
| Blood draw for RCR analysis [5] | X | | X | | | X | | X | | X | | X | X |
| Targeted AE/SAEs [6] | X | X | X | X | X | X | | | | | | | |
| Targeted concomitant medication [7] | X | X | X | X | X | X | | | | | | | |
| Subsequent therapy for NHL[8] | X | X | X | X | X | X | X | X | X | X | X | X | X |

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.
3. Subjects will continue to provide samples for CBC w/diffs, lymphocyte subsets and anti-CD19 CAR T cells through Month 24
4. Anti-axicabtagene ciloleucel antibody samples: refer to Section 7.11
5. RCR samples: collect and measured at Month 3, 6 and 12, then collect yearly for up to 15 years. Yearly samples will only be analyzed if positive at Month 3, 6, or 12.
6. Targeted AEs/SAEs will be collected for 24 months or until disease progression (whichever occurs first)
7. Targeted concomitant medications will be collected for 24 months or until disease progression (whichever occurs first)
8. Subsequent therapy administered after axicabtagene ciloleucel infusion for a subjects' 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.

# 8. SUBJECT WITHDRAWAL

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

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

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

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

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

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

## 8.1. Reasons for Removal from Treatment

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

- Adverse Event
- Subject request
- Product not available
- Lost to Follow-up
- Death
- Decision by sponsor

## 8.2. Reasons for Removal from Study

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

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

# 9. SAFETY REPORTING

## 9.1. Adverse Events

An adverse event 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 adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

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

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

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., B-Cell Lymphoma).

For situations when an adverse event or serious adverse event is due to the disease under investigation report the signs and symptoms. Worsening of signs and symptoms of the malignancy under study should also be reported as adverse events in the appropriate section of the CRF.

The investigators clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol required therapies or the study due to an adverse event, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

## 9.2. Reporting of Adverse Events

The investigator is responsible for **reporting** all adverse events observed by the investigator or reported by the subject that occur from enrollment (ie, commencement of leukapheresis) through 3 months after treatment with axicabtagene ciloleucel infusion **or until the initiation of another anti-cancer therapy, whichever occurs first**. After 3 months, targeted adverse events including (eg, neurological, hematological, infections, autoimmune disorders, and secondary malignancies) will be monitored and reported for 24 months after treatment with axicabtagene ciloleucel or until disease progression, whichever occurs first.

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

The investigator must address the below for adverse events:

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

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (http://ctep.cancer.gov). Cytokine Release Syndrome events will also be reported using the grading scale outlined in Section 6.4.

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

The investigator is expected to follow reported adverse events until stabilization or resolution. If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events 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 adverse event if it is a change from baseline and meets any of the following criteria:

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

### 9.3. Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- 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

An adverse event 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 a serious adverse event. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event 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 adverse event recorded on the electronic CRF.

## 9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 3 months after the axicabtagene ciloleucel infusion **or until the initiation of another anti-cancer therapy, whichever occurs first**. After 3 months, only serious targeted adverse events (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) observed by the investigator or reported by the subject will be reported for 24 months after axicabtagene ciloleucel infusion or until disease progression, whichever occurs first. For subjects who screen fail or are enrolled but do not receive axicabtagene ciloleucel, the reporting period for serious adverse events ends 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy).

Serious events that the investigator assesses as related to axicabtagene ciloleucel should be reported regardless of the study period.

All SAEs must be submitted via email to safety_fc@gilead.com within 24 hours following the investigator's knowledge of the event and using a SAE Report Form.

Subsequently, all serious adverse events will be reported to the health authorities per local reporting guidelines.

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

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

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

## 9.5. Reporting Deaths

Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression of underlying lymphoma should be recorded as serious adverse events (SAEs) with the preferred term "B-cell lymphoma" and must be reported immediately to the sponsor. Death is an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded on the AE form. The term "unexplained death" should be captured if the cause of death is not known. However, every effort should be made to capture the established cause of death, which may become available later on (eg, after autopsy). Deaths during the post-study survival follow-up due to underlying cancer should be recorded only on the Survival Status CRF.

## 9.6. Diagnosis versus Signs and Symptoms

For adverse events, 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 signs and symptoms will be captured on the CRF AE form. For signs and symptoms of the underlying cancer, the signs and symptoms should be captured. However, on the AE form, the investigator should state that these signs and symptoms are due to the underlying disease.

## 9.7. Pregnancy and Lactation

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

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

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

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol required therapies report the lactation case to the key sponsor contact.

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.

Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator's knowledge of the event.

## 9.8. Hospitalization and Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event as described in Section 9.4.

The following hospitalization scenarios are not considered to be serious adverse events:

- 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 adverse event. A vital sign result must be reported as an adverse event 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 adverse event. 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

Phase 1 Study

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 axicabtagene ciloleucel DLT and review of serious adverse events.

Dose-limiting toxicity is defined as the following axicabtagene ciloleucel-related events with onset within the first 30 days following axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 35 days from the day of cell transfer
- Any axicabtagene ciloleucel-related adverse event requiring intubation, including Grade 4 confusion requiring intubation for airway protection is considered to be a DLT.

- All other Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following conditions which are not considered DLTs:

- Aphasia/dysphasia or confusion/cognitive disturbance which resolves to Grade 1 or less within 2 weeks and to baseline within 4 weeks

- Fever Grade 3

- Myelosuppression (includes bleeding in the setting of platelet count less than 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above

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

- Hypogammaglobulinemia Grade 3 or 4

As noted in Section 6.4 CRS will be graded according to a revised grading system (Lee et al, 2014). Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT.

During Phase 1, approximately 6 to 24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens.

Subjects in each cohort will be evaluated for DLTs within the first 30 days following the completion of their respective axicabtagene ciloleucel infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in Section 10.5 . The SRT will make recommendations based on the incidence of DLT and overall safety profile of the axicabtagene ciloleucel regimen. If the subject incidence of DLT is ≤ 1 of 6 subjects, Cohort B1 may be explored or 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 2 of the 6 enrolled subjects present with a protocol defined DLT during Phase 1, the SRT may recommend enrolling 2 additional sets of 3 subjects (up to 12 subjects in total) at the same dose that was administered in the first 6 subjects. In this scenario, progression to an additional cohort or to Phase 2 of the study will proceed if ≤ 2 of the first 9 or if ≤ 3 of the 12 subjects present with a DLT.

If the subject incidence of DLT is > 2/6, > 3/9, or > 4/12 subjects, other axicabtagene ciloleucel regimens may be explored in an additional 6 to 12 subjects (Figure 3). The same DLT rules apply as above.

## 9.11. Data Safety Monitoring Board

Phase 2 Pivotal Study

An independent DSMB will meet during the Phase 2 pivotal portion of the study when 20 and 50 subjects in the mITT set of Cohort 1 have had the opportunity to complete the 3-month disease assessment. The DSMB will review safety and efficacy data and be chartered to make trial conduct recommendations based on an analysis of risk vs. benefit.

Phase 2 Safety Management Study

The DSMB will also meet to review safety data when 20 subjects in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days, respectively. The DSMB may meet more often as needed. In addition, Kite Pharma or delegate will submit SAEs or suspected unexpected serious adverse reactions (SUSARs) to the DSMB chair for risk benefit analysis. The DSMB Chair will review reported SAEs at least monthly and SUSARs as soon as received.

## 9.12. Criteria to Pause Enrollment

Phase 2 Pivotal Study

As part of its oversight of the study, the DSMB also will assess criteria to pause enrollment after 10, 20, 30, and 50 subjects in the Phase 2 pivotal portion of the study have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria is met:

1) Subject incidence of Grade 5 axicabtagene ciloleucel-related adverse events within 30 days is > 10%.

   or

2) Subject incidence of the following Grade 4 axicabtagene ciloleucel-related adverse events lasting more than 7 days is > 33%:

   - Neurologic toxicities
   - CRS (per Lee 2014 criteria) (Lee et al, 2014)
   - Other non-hematological serious adverse event
   - Infection (treatment-related)

# 10. STATISTICAL CONSIDERATIONS

The primary objective of the Phase 1 Study is to evaluate the safety of axicabtagene ciloleucel regimens. The primary objective of the pivotal Phase 2 portion is to evaluate the efficacy of axicabtagene ciloleucel, as measured by ORR in subjects with DLBCL, PMBCL, and TFL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints. Inferential testing will only be performed for efficacy for Phase 2 pivotal study Cohort 1 and Cohort 2. For the Phase 2 safety management study, Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, the primary objective is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, **or prophylactic steroids** on the rate and severity of CRS and neurologic toxicities.

## 10.1. Hypothesis

Phase 2 pivotal study Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR to axicabtagene ciloleucel in Cohort 1 and Cohort 2 is significantly greater than 20%.

Phase 2 safety management study Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**: No hypothesis will be tested in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6,** which will be used to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, **or prophylactic steroids** on the rate and severity of CRS and neurologic toxicities.

## 10.2. Study Endpoints

### 10.2.1. Primary

Phase 1 study: Incidence of adverse events defined as DLT.

Phase 2 pivotal study: ORR, defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by the study investigators. All subjects who do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

Phase 2 safety management study: incidence and severity of CRS and neurologic toxicities.

### 10.2.2. Secondary

**Duration of response** (DOR): Among subjects who experience an objective response, DOR is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) or death regardless of cause. 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.

ORR among subjects in Phase 1 will be summarized.

ORR per **Independent Radiological Review Committee (**IRRC**)** (Phase 2): ORR per IRRC is defined as the incidence of either a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by the IRRC. All subjects that do not meet the criteria for an objective response by the analysis data cutoff date will be considered non-responders.

Progression-free Survival (PFS): PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date.

OS: OS is defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date.

Incidence of adverse events and clinical significant changes in safety lab values.

Incidence of anti-axicabtagene ciloleucel antibodies, levels of anti-CD19 CAR T cells in blood, and levels of cytokines in serum will be summarized.

Additional Phase 2 Safety management study secondary endpoints include the following:

- ORR for subjects treated in the safety management study Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**
- Changes over time in the EQ-5D scale score and EQ-5D VAS score for subjects treated in Cohort 3, Cohort 4, Cohort 5 **and Cohort 6**

### 10.2.3. Exploratory Endpoints

- ORR and duration of second response among subjects retreated with axicabtagene ciloleucel (Section 7.13.10).
- ORR and DOR as determined by IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2014).
- **Biomarkers** based on assessment of blood cells, tumor cells and the proposed actions of the investigational product.

## 10.3. Sample Size Considerations

The anticipated enrollment in this study is approximately **268** to **286** subjects.

Phase 1 Study: Six to 24 subjects will be enrolled into each cohort in Phase 1 of this study.

If the study proceeds to Phase 2 pivotal study, approximately 72 subjects will be enrolled into Cohort 1, and approximately 20 subjects will be enrolled into Cohort 2.

In the Phase 2 safety management study, approximately 40 subjects will be enrolled into Cohort 3, approximately 40 subjects will be enrolled and dosed into Cohort 4, approximately 50 subjects will be enrolled and dosed into Cohort 5**, and approximately 40 subjects will be enrolled and dosed into Cohort 6**.

ORR and all analyses based on the objective response (objective response, duration of response, progression-free survival) in the Phase 1 and Phase 2 portions of the study will be based on a mITT population consisting of all subjects who receive the target dose of axicabtagene ciloleucel.

Inferential testing will be performed only for efficacy for Phase 2 pivotal study Cohort 1 and Cohort 2. For Cohort 3, Cohort 4, Cohort 5, **and Cohort 6,** the primary objective will be to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, **or prophylactic steroids** on the rate and severity of CRS and neurologic toxicities. ORR with axicabtagene ciloleucel treatment in subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** will be a secondary endpoint, and the analysis will be descriptive.

### 10.3.1. Phase 2 Pivotal Study, Cohort 1, and Cohort 2

This study uses a single arm design to test for an improvement in response rate in the DLBCL cohort (approximately n=72) and in Cohorts 1 and 2 combined (n=92). For the test of efficacy this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha level of 0.025.

The overall 1-sided alpha level of 0.025 will be divided between the inference on Cohort 1 and the inference in Cohorts 1 and 2 combined using the methodology described in (Song and Chi 2007; Wang et al, 2007). The objective response for Cohort 1 will be tested at a 1-sided alpha level of 0.0220 and the objective response in Cohort 1 and 2 combined will be tested at a 1-sided alpha level of 0.0075.

Within Cohort 1, 2 interim and 1 primary analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only. This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to Phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early demonstration of efficacy. This interim analysis is based on a Pocock boundary of the Lan-DeMets family of alpha spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the likelihood of achieving the criteria for early

efficacy is 84%. If the criteria for early efficacy are not met at this analysis, the planned primary analysis of Cohort 1 will occur when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion.

- The primary analysis of Cohort 1 will occur after 72 subjects in the mITT set have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. The nominal alpha level for the assessment of efficacy at the primary analysis is 0.011.

Accrual to the study will continue during interim analysis 1 and interim analysis 2 of Cohort 1.

For Cohorts 1 and 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set in Cohort 1 and 20 subjects in the mITT set in Cohort 2 have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion. This testing will be performed at a 1-sided alpha level of 0.0075. Descriptive confidence intervals about the ORRs within Cohorts 1 and 2 will be presented with the inferential analysis of Cohorts 1 and 2 combined.

As indicated above, inferential testing of Cohort 1 will occur when 72 subjects in the mITT set in Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 72) enrolled into Cohort 1 will be analyzed descriptively. Similarly, inferential testing of Cohorts 1 and 2 will occur when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set of Cohort 2 have had the opportunity to be followed for 6 months following the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 92) enrolled into Cohorts 1 and 2 will be analyzed descriptively.

The derivation of the alpha levels for the test of Cohort 1 and the overall study population were originally obtained under the assumption of 40 subjects enrolled into Cohort 2. These original derivations are retained in this protocol amendment as they result in a more conservative alpha level for the test of Cohort 1.

This procedure preserves the designated alpha level (1-sided) of 0.025 and has ≥ 90% power. Simulation (10,000 replicates) via R version 3.1.0 and EAST version 6.3 were used to evaluate the operating characteristics of this design.

### 10.3.2. Phase 2 Safety Management Study

The primary objective of Phase 2 safety management study Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, **or prophylactic steroids** on the rate and severity of CRS and neurologic toxicities. The assessment of ORR is a secondary objective, and the analysis will be descriptive.

## 10.4. Statistical Assumptions

Phase 1 Study

The primary endpoint for the Phase 1 portion of the study is the incidence of DLT.

Phase 2 Pivotal Study

Cohorts 1 and 2 of this trial will enroll subjects with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

Treatment outcomes for subjects refractory to primary therapy or non-responsive to second line therapy are provided in Section 2.1, Table 1. As indicated, the response to salvage therapy for these patients ranged from 0% to 26%. Additionally, a retrospective review of data in refractory DLBCL from 4 institutions (Crump et al, 2017) indicate a response rate of 26% among 636 patients with refractory disease. Based on these data, it is anticipated that the historical control for the ORR in the chemo-refractory population targeted in this study will be approximately 20%.

Phase 2 Safety Management Study

**Analyses** of the safety and efficacy endpoints will be descriptive, with no formal statistical testing being performed. Subject incidence rates of treatment-emergent CRS, neurologic toxicities, axicabtagene ciloleucel-related adverse events, and ORRs will be summarized by cohort. DOR, PFS, and OS will also be summarized by cohort.

## 10.5. Analysis Subsets

### 10.5.1. Phase 1 Study

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

- administered as a single infusion at a target dose of $2 \times 10^6$ anti-CD19 CAR T cells/kg (± 20%). For subjects weighing greater than 100 kg, a maximum flat dose of $2 \times 10^8$ anti-CD19 CAR T cells will be administered. A minimum dose of $1 \times 10^6$ anti-CD19 CAR T cells/kg may be administered; or

- administered as a single infusion at a target dose of $1 \times 10^6$ anti-CD19 CAR T cells/kg (± 20%) in the Phase 2 portion of the study. In this case, for subjects weighing greater than 100 kg, a maximum flat dose of $1 \times 10^8$ anti-CD19 CAR T cells will be administered. A minimum dose of $0.5 \times 10^6$ anti-CD19 CAR T cells/kg may be administered.

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

- received the target and were followed for at least 30 days after the anti-CD19 CAR T cell infusion; or

- received a dose of anti-CD19 CAR T cells lower than the target for that cohort and experienced a DLT during the 30 day post-infusion period.

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

Safety set: the safety set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

### 10.5.2. Phase 2 Study

In the Phase 2 portion of the study (including the Phase 2 pivotal study and SMS), subjects are to be dosed at a target of $2 \times 10^6$ anti-CD19 CAR T cells/kg. A minimum dose of $1 \times 10^6$ anti-CD19 CAR T cells/kg may be administered. For subjects weighing greater than 100 kg, a maximum flat dose of $2 \times 10^8$ anti-CD19 CAR T cells will be administered. Subjects are considered to have received the target dose if they receive $1 \times 10^6$ anti-CD19 CAR T cells/kg up to $2 \times 10^6$ anti-CD19 CAR T cells/kg or, if the subject weighs more than 100 kg, the subject receives $2 \times 10^8$ anti-CD19 CAR T cells.

Modified Intent-to-Treat Set: the mITT set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a dose of at least $1 \times 10^6$ anti-CD19 CAR T cells/kg.

This analysis set will be used for all analyses of objective response and endpoints based on objective response (objective response, duration of response, progression-free survival) for both the Phase 1 and Phase 2 portions of the study (including both pivotal and SMS).

Safety analysis set: the safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

Full Analysis set (FAS): the full analysis set will consist of all enrolled subjects and will be used for the summary of subject disposition, sensitivity analyses of ORR and DOR, and subject listings of deaths.

## 10.6. Access to Individual Subject Treatment Assignments

This is a single arm, open-label study and subjects and investigators will be aware of treatment received. Data handling procedures for the Phase 2 portion of the study will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan, DSMB charter, and Trial Integrity Document.

## 10.7. Interim Analysis

### 10.7.1. Interim Analysis and Early Stopping Rules

Phase 1 Study

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

Phase 2 Pivotal Study

An independent DSMB will be formed to review accumulating safety and efficacy data 2 times during the Phase 2 pivotal study, when 20 and 50 subjects in the mITT set in Cohort 1 have had the opportunity to complete the 3-month disease assessment.

The DSMB will also monitor criteria to pause enrollment (see Section 9.12).

Phase 2 Safety Management Study

The DSMB will review safety data when 20 subjects treated in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** have had the opportunity to be followed for 30 days, respectively.

### 10.7.2. Safety Interim Analysis

The DSMB will review AE and SAE information on a regular basis throughout subject treatment in Phase 2 of the study. The DSMB may request additional safety data or **to modify** the study conduct. The sponsor may request additional reviews by the DSMB if safety concerns are identified. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

### 10.7.3. Efficacy Interim Analysis

Phase 2 Pivotal Study

Within Cohort 1, two interim analyses will be performed.

- Interim analysis 1 will be conducted after 20 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will be for futility only. This futility analysis is based on a rho (parameter 0.35) beta spending function, with a nominal alpha level for the assessment of futility of 0.393. If the criteria for futility are not met, accrual to Phase 2 will continue. Under the null hypothesis, the likelihood of stopping for futility at this analysis is 63%.

- Interim analysis 2 will be conducted after 50 subjects in the mITT set have had the opportunity to be evaluated for response 3 months after the axicabtagene ciloleucel infusion. This interim analysis will assess early stopping for efficacy. This interim analysis is based on a Pocock boundary of the of the Lan-DeMets family of alpha

spending functions. The nominal alpha level for the assessment of efficacy for this analysis is 0.017. Under the alternative hypothesis, the likelihood of achieving the criteria for early efficacy is 84%. If the criteria for early efficacy are not met at this analysis, the planned primary analysis of Cohort 1 will occur when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion.

Phase 2 Safety Management Study

There is no planned efficacy interim analysis for this portion of the study.

## 10.8. Planned Method of Analysis

Phase 1 Study

Descriptive analysis of the Phase 1 portion of the study may occur at any time.

Phase 2 Pivotal Study

The primary efficacy analyses of Cohort 1 will be performed when 72 subjects in the mITT set of Cohort 1 have had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The primary analysis of Cohorts 1 and 2 combined will be performed when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set of Cohort 2 have had the opportunity to be evaluated for response at 6 months after the target axicabtagene ciloleucel infusion. Additional analyses may occur after the primary analysis. These additional analyses will be descriptive and will occur after inferential testing has been performed. The final analysis will occur when all subjects have completed the study.

The primary endpoint of ORR for all analyses (futility, interim, and primary) will be based on investigator review of disease assessments in the mITT set. For Cohorts 1 and 2, sensitivity analyses of ORR based on central radiologic review of disease assessments will be performed.

Analyses of efficacy endpoints will be summarized by study phase, for Cohort 1 alone, for Cohort 1 and Cohort 2 combined, and for Cohort 3 alone. Analyses of safety endpoints will be evaluated by study phase, cohort, Cohort 1 and 2 combined.

Phase 2 Safety Management Study

The primary analysis of Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** will occur after all treated subjects in each cohort have had the opportunity to be followed for 6 months, respectively. The ORR in Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** will be based on investigator review of disease assessment in the mITT set. No central radiologic review of disease assessment will be performed for these cohorts.

Descriptive analyses of the Phase 2 SMS Cohort 3, Cohort 4, Cohort 5, **and Cohort 6** may occur at any time.

### 10.8.1. Objective Response Rate

The incidence of objective response and exact 2-sided 95% confidence intervals will be generated. For the Phase 2 pivotal study, Cohort 1 and Cohort 2, an exact binomial test will be used to compare the observed response rate to a response rate of 20%.

### 10.8.2. Duration of Response

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for duration of response. Estimates of the proportion of subjects in response at 3-month intervals from the first response will be provided**.** The competing-risk analysis method (Pepe 1991; Fine and Gray 1999) may be used to estimate the cumulative incidence of relapse. The cumulative incidence of relapse in the presence of non-disease related mortality (the competing risk) **may** be estimated along with 2-sided 95% confidence intervals at 3-month intervals.

### 10.8.3. Progression-free Survival

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

### 10.8.4. Overall Survival

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

### 10.8.5. Safety

Subject incidence rates of adverse events including all, serious, fatal, CTCAE version 4 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.

For Cohort 3, Cohort 4, Cohort 5, **and Cohort 6**, the incidences and severity of CRS and neurologic toxicities may be compared to the rates in Cohort 1 and Cohort 2 combined with a binomial test.

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

### 10.8.6. Long-term Data Analysis

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

# 11. REGULATORY OBLIGATIONS

## 11.1. Independent Review Board/Independent Ethics Committee

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

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

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

## 11.2. Subject Confidentiality

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

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

For reporting of serious adverse events, subjects will be identified by their respective subject identification number, initials and data of birth or year of birth (as per their local reporting requirements for both initials and date of birth)

Per federal regulations and International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) guidelines, investigators and institutions are required to permit authorization to the sponsor, contract research organization (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 under the following criteria:

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

# 12. PROTOCOL AMENDMENTS AND TERMINATION

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

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

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

# 13. STUDY DOCUMENTATION AND ARCHIVE

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

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

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

- Subject content including ICFs and subject 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 and the investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

# 14. STUDY MONITORING AND DATA COLLECTION

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

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

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

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

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

# 15. PUBLICATION

Authorship of publications from data generated in study KTE-C19-101 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013) which states:

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

When a large, multicenter group has conducted the work, the group should identify the individual who accepts 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 for review and approval. The study contract between the institution, principal investigation and Kite Pharma or its delegate will outline the requirements for publication review.

# 16. COMPENSATION

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

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# 18. APPENDICES

Appendix A Revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007)
Appendix B Monitoring of subjects after IP administration per country regulatory agencies:

## Appendix A Revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007)

Complete Remission (CR): CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

- Typically FDG-avid lymphoma (large cell, mantle cell and follicular lymphomas are all typically FDG-avid): in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

- The spleen and/or liver, if considered to be enlarged before therapy on basis of physical exam or CT scan, must should be normal size on CT scan and not be palpable on physical examination and nodules thought to represent lymphoma must no longer be present.

- A bone marrow aspirate and biopsy is performed only when the patient had bone marrow involvement with lymphoma prior to therapy or if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma after treatment. 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. The biopsy core sample must be a minimum of 20 mm in length.

Partial Remission (PR): PR requires all of the following:

- ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. Dominant nodes or nodal masses should be clearly measurable in at least 2 perpendicular dimensions, should be from different regions of the body if possible and should include mediastinal and retroperitoneal nodes if possible.

- No increase in size of nodes, liver or spleen and no new sites of disease.

- If multiple splenic and hepatic nodules are present, they must regress by ≥ 50% in the SPD. There must be a > 50% decrease in the greatest transverse diameter for single nodules.

- Bone marrow is irrelevant for determination of a PR. If patient has persistent bone marrow involvement and otherwise meets criteria for CR the patient will be considered a PR.

- Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET scan should be positive in at least one previously involved site. Note: in subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated in subjects with one or at most two residual masses that have regressed by 50% on CT scan.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PET should be positive in typically FDG-avid lymphomas.

Progressive Disease:

Defined by at least one of the following:

- $\geq$ 50% increase from nadir in the sum of the products of at least two lymph nodes, or if a single node is involved at least a 50% increase in the product of the diameters of this one node.

- Appearance of a new lesion greater than 1.5 cm in any axis even if other lesions are decreasing in size

- Greater than or equal to a 50% increase in size of splenic or hepatic nodules

- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

- Lesions should be PET positive in typically FDG-avid lymphomas unless the lesion is too small to be detected by PET (< 1.5 cm in its long axis by CT)

## Appendix B Monitoring of subjects after IP administration per country regulatory agencies:

Germany:

The post-infusion monitoring of subjects, described in Section 7.13.7.2 in this protocol, will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 11, column "IP administration period, 1-7". The subject may stay hospitalized or return to the clinic daily for this extended monitoring at the discretion of the investigator.

The daily monitoring will include vital signs (see Section 7.4), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11), and neurological assessment**.** Any observed toxicity will be managed according to Section 6.4 of this protocol.

**France:**

**The post-infusion monitoring of subjects in this protocol will be extended by monitoring on Day 8, Day 9, and Day 10, according to procedures outlined in Table 11, column "IP administration period, 1-7." The L'Agence nationale de sécurité du médicament et des produits de santé (ANSM) recommends a 10-day hospitalization after infusion of any CAR T-cell product.**

**The daily monitoring will include vital signs (see Section 6.4), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11), and neurological assessment. Any observed toxicity will be evaluated according to Section 6.4 of this protocol.**