# CLINICAL STUDY PROTOCOL

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| Protocol Title: | A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7) |
| Protocol Number: | KTE-C19-107 (ZUMA-7) |
| USAN/INN: | Axicabtagene ciloleucel |
| Company Code: | KTE-C19 |
| IND Number: | 016278 |
| EudraCT Number: | 2017-002261-22 |
| Sponsor Name and Address: | Kite Pharma, Inc.<br>2400 Broadway<br>Santa Monica, CA 90404<br>United States of America |
| Contact Information: | The medical monitor name and contact information is provided on the Key Study Team Contact List |
| Protocol Version/Date: | Original: 22 May 2017 |
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| Country-specific Requirements: | Country-specific requirements are listed in Appendix D |

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

## PROTOCOL SYNOPSIS

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| **Title:** | A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7) |
| **Indication:** | Adult subjects with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). |
| **Study Design:** | This is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus standard of care therapy (SOC) in subjects with r/r DLBCL. Adult subjects with r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOC. Randomization will be stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (IPI) (0 to 1 vs 2 to 3) as assessed at the time of screening.<br>For subjects randomized to the control arm of the study, SOC will consist of a protocol-defined, platinum-based salvage combination chemotherapy regimen. Subjects who respond to second-line chemotherapy (partial response [PR] or complete response [CR]) should proceed to high-dose therapy (HDT) and autologous stem cell transplant (ASCT).<br>An independent Data Safety Monitoring Board (DSMB) will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed. Refer to Section 9.9 for further details.<br>For study requirements assigned to each study arm, please refer to the schedule of assessments (SOA) and Section 7 for details.<br>A study schema is drawn out and described at the end of the protocol synopsis section. |

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| **Study Objectives:** | Primary Objective<br>• To determine if axicabtagene ciloleucel is superior to SOC as measured by event-free survival (EFS), as determined by blinded central review<br>Secondary Objectives<br>• To evaluate the effect of axicabtagene ciloleucel compared to SOC on objective response rate (ORR), as determined by blinded central review<br>• To evaluate the effect of axicabtagene ciloleucel compared to SOC on overall survival (OS)<br>• To evaluate the effect of axicabtagene ciloleucel compared to SOC on progression-free survival (PFS)<br>• To evaluate the effect of axicabtagene ciloleucel compared to SOC on duration of response (DOR) and duration of complete response among responding subjects, as determined by blinded central review<br>• To evaluate the safety of axicabtagene ciloleucel compared to SOC<br>• To evaluate the effect of axicabtagene ciloleucel on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC |
| | CCI [redacted] |
| **Hypothesis:** | Axicabtagene ciloleucel will prolong EFS compared to SOC therapy in adult subjects with relapsed/refractory DLBCL. The hypothesized treatment effect corresponds to a 50% improvement in EFS. |
| **Primary Endpoint:** | Event-free Survival (EFS): EFS is defined as the time from randomization to the earliest date of disease progression per the Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy, or death from any cause. Subjects not meeting the criteria for these events by the analysis data cutoff date will be censored. For the primary analysis of EFS, disease progression events and censoring times will be determined by blinded central review. Events of new therapy and death will be based on the clinical trial database. |

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| **Secondary Endpoint(s):** | Key secondary endpoints (in order of hierarchical testing)<br>• Objective response rate<br>• Overall survival<br>Secondary endpoints<br>• EFS based on investigator disease assessments<br>• Modified EFS based on blinded central review and on investigator disease assessments<br>• Progression-free survival<br>• Duration of response and complete response<br>• Incidence of adverse events and clinically significant changes in safety lab values, including antibodies to axicabtagene ciloleucel<br>• Changes from screening to post baseline in the global health status QoL scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30)<br>• Changes from screening to post baseline in the Euro-QOL, Five Dimensions, Five Levels (EQ-5D-5L) index and visual analog scale (VAS) scores |
| CCI | |
| **Sample Size:** | Approximately 350 subjects |
| **Study Eligibility:** | Please refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria. |
| **Treatment:** | Axicabtagene ciloleucel arm<br>Subjects randomized to the axicabtagene ciloleucel arm of the study will receive a 3-day conditioning chemotherapy regimen consisting of fludarabine 30 mg/m$^2$/day and cyclophosphamide 500 mg/m$^2$/day on day -5 to day -3 followed by 2 rest days (day -2 and day -1).<br>A single infusion of axicabtagene ciloleucel administered intravenously at a target dose of 2 x 10$^6$ anti-CD19 CAR T cells/kg on day 0. |

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| **Treatment:** | Standard of Care arm<br>• Subject will receive a second-line combination chemotherapy regimen (R-ICE, R-DHAP, R-ESHAP, or R-GDP) as selected by the treating investigator.<br>• Subjects responding to second-line combination chemotherapy after 2 or 3 cycles (PR or CR) should proceed to high-dose therapy (HDT) and autologous stem cell transplant (ASCT).<br>• Peripheral stem cell collection, HDT, and ASCT infusion will be per institutional or regional guidelines. |
| **Procedures:** | As outlined in the SOAs, subjects will undergo the following procedures: collection of informed consent; medical history; physical exam; bone marrow biopsy; disease staging, including a baseline PET-CT scan; and blood draws for lactate dehydrogenase levels, complete blood count (CBC), and blood chemistries. Subjects will also undergo baseline echocardiogram (ECHO) and electrocardiogram (ECG) assessments and Eastern Cooperative Oncology Group (ECOG) performance status. Women of childbearing potential will undergo a urine or serum pregnancy test.<br>Subjects randomized to the axicabtagene ciloleucel arm will undergo leukapheresis for the collection of peripheral blood mononuclear cells necessary for axicabtagene ciloleucel manufacturing. Conditioning chemotherapy will be followed by 2 rest days and then infusion of axicabtagene ciloleucel. Subjects will be under an observation period for at least 7 days after axicabtagene ciloleucel infusion to monitor for and manage any adverse events, unless otherwise required by country regulatory agencies (refer to Appendix D). Blood draws for the analysis of anti-CD19 CAR T-cell levels will be performed. Additional blood draws for cytokines, anti-axicabtagene ciloleucel antibodies, and replication-competent retrovirus (RCR) may be performed as clinically indicated. Treatment with axicabtagene ciloleucel is intended to be definitive therapy and not a bridge to ASCT.<br>Subjects randomized to the SOC arm will receive investigator's choice of second-line combination chemotherapy from the protocol-defined options. Up to 3 cycles (6 to 9 weeks) of combination chemotherapy will be administered every 2 to 3 weeks. Subjects with a PR or CR to second-line therapy should proceed to HDT-ASCT. Peripheral stem cell mobilization and leukapheresis will be performed according to institutional guidelines after the second or third cycle of second-line therapy to obtain a minimum target of $2 \times 10^6$ CD34+ hematopoietic stem cells per kilogram. HDT-ASCT will be performed per institutional guidelines.<br>Routinely throughout the conduct of the study, all subjects will be asked to report concomitant medications and adverse events, report subsequent lymphoma therapy, answer patient reported outcomes (PROs), and will have routine disease assessments as outlined in the SOAs. |

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| | Independent of the randomized treatment arm, study procedures and disease assessments will occur at the same protocol-defined time points.<br>For details for all study requirements, refer to Section 7 and the SOAs. |
| **Duration of Study Participation** | The duration of participation for individual subjects will vary depending on a subject's screening requirements, response to treatment, potential for re-treatment, survival, and timing of the transition to a separate Kite Long-term Follow-up (LTFU) study.<br>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 study will take approximately 5 years to complete for those randomized to the SOC arm and approximately 15 years to complete for those randomized to the axicabtagene ciloleucel arm. |
| **Data Safety Monitoring Board (DSMB):** | An independent DSMB will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed. Refer to Section 9.9 for further details. |
| **Statistical Considerations:** | The primary goal of the statistical analysis is to determine if there is a statistically significant improvement in event-free survival (EFS) between the treatment groups. Approximately 350 subjects (175 per arm) will be randomized to attain 250 EFS events. Randomization will be stratified by response to first-line therapy and second-line age-adjusted IPI assessed at the time of screening. Efficacy analyses will be conducted on all randomized subjects analyzed according to randomized treatment arm. Safety analyses will be conducted on all subjects who receive protocol-specified therapy analyzed according to treatment actually received. The study will have an overall alpha of 2.5% with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints will follow a hierarchical scheme. EFS will be tested first at the primary EFS analysis. Conditional on a statistically significant improvement in EFS, ORR will be tested at the 2.5% level at the time of the primary EFS analysis. Conditional on a statistically significant improvement in EFS and ORR, OS will be tested up to 3 times at an overall alpha level of 2.5%. The primary analysis of OS will occur when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized. A first interim analysis of OS will occur at the time of the primary EFS analysis and a second interim analysis when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized. A spending function of the Rho family will be used to allocate the alpha between the 2 interim analyses of OS and the primary analysis of OS. Additionally, one interim futility analysis of EFS will be conducted after 135 EFS events have been observed. Stratified (randomization factors) log-rank tests will be used to |

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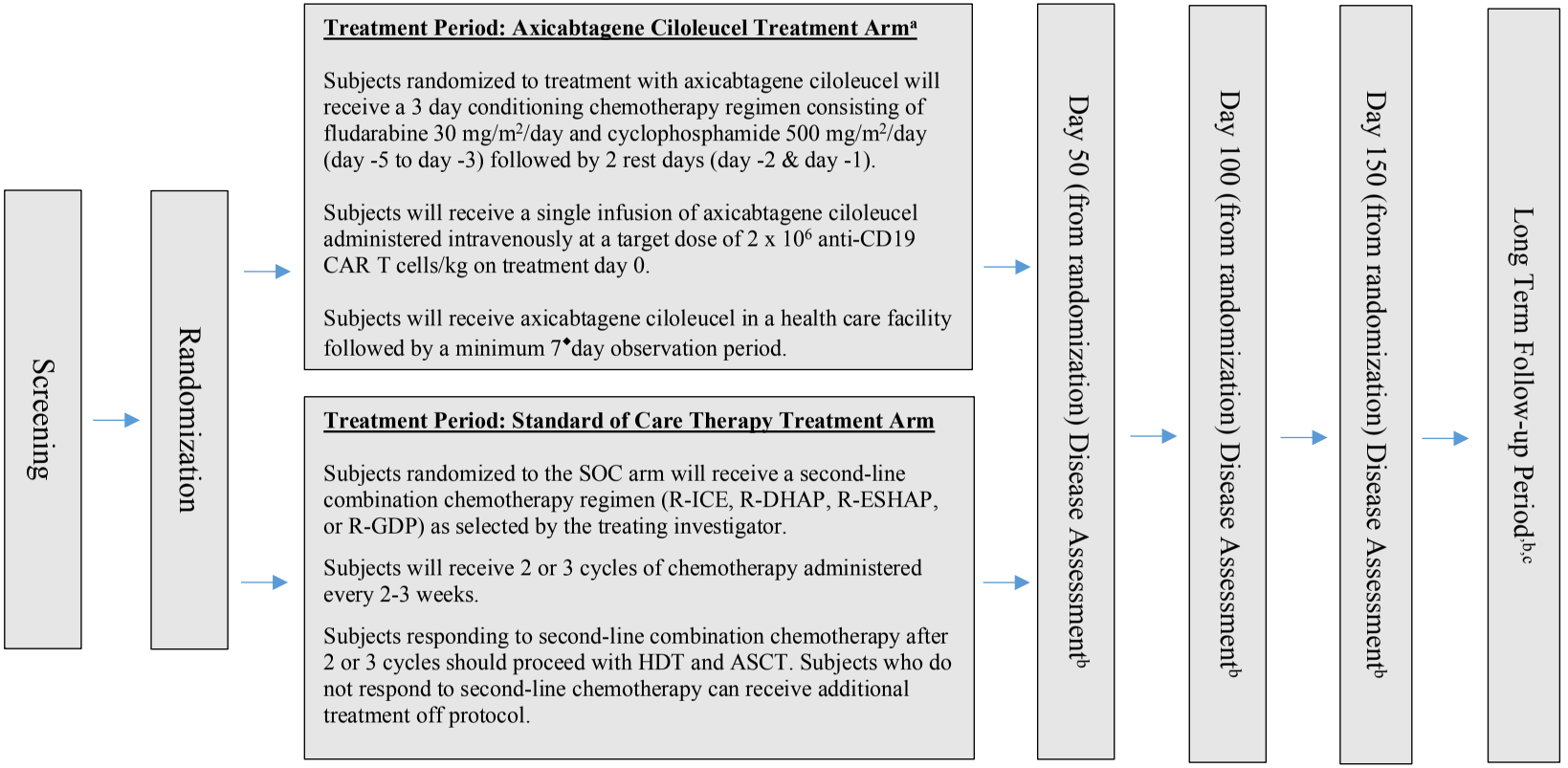
| | test the null hypothesis of no difference in EFS and OS using an overall 1-sided alpha level of 2.5%. A stratified (randomization factors) Cochran-Mantel-Haenszel test will be used to test ORR at an overall 1-sided alpha level of 2.5%.<br>For a full description of statistical analysis methods, refer to Section 10. |

## STUDY SCHEMA




a **Bridging therapy:** At the discretion of the investigator, corticosteroid bridging therapy may be considered for subjects with high disease burden at screening. Refer to Section 6.2.4.2 for details.

b **Disease Assessments:** Calculated from the day of randomization and not the date of dosing with axicabtagene ciloleucel or SOC therapy. Independent of the randomized treatment arm, study procedures and disease assessments will occur at the same protocol defined time points.

c After completing at least 60 months of assessments in Study KTE-C19-107, subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will complete the remainder of the 15-year follow-up assessments in a separate LTFU study after providing informed consent. Refer to Section 3.5

◆ **Minimum observation period: 7 days unless otherwise required by country regulatory agencies (refer to Appendix D).**

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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 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 |
| Axicabtagene ciloleucel | Autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3ζ chimeric antigen receptor |
| CAR | Chimeric antigen receptor |
| CBC | Complete blood count |
| CLL | Chronic lymphocytic leukemia |
| CMR | Complete metabolic response |
| CNS | Central nervous system |
| CR | Complete response |
| CRF | Case Report Form |
| CRP | C-reactive protein |
| CRO | Contract Research Organization |
| CRR | Complete radiologic response |
| CRS | Cytokine release syndrome |
| CSF | Cerebrospinal fluid |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLBCL | Diffuse large B-cell lymphoma |
| DOR | Duration of response |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EEG | Electroencephalogram |
| EFS | Event-free survival |
| End of study (primary completion) | Defined as when the last subject has undergone an assessment for the purpose of the event driven primary analysis |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (QLQ-C30) |
| EQ-5D-5L | Euro-QOL, Five Dimensions, Five Levels |
| FAS | Full analysis set |

| Abbreviation | Definition |
|---|---|
| FL | Follicular lymphoma |
| GCP | Good Clinical Practice |
| GP | General practitioner |
| HCP | Healthcare provider |
| HDT | High-dose therapy |
| HEENT | Head, ears, eyes, nose, throat |
| HIV | Human immunodeficiency virus |
| HLH | Hemophagocytic lymphohistiocytosis |
| HRQoL | Health-related quality of life |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| IHC | Immunohistochemistry |
| IL | Interleukin |
| IP | Investigational product |
| IPI | International Prognostic Index |
| IPM | Investigational Product Manual |
| IRB/IEC | Institutional Review Board/Independent Ethics Committee |
| IV | Intravenous |
| IXRS | Interactive Voice/Web (X) Response System |
| LDH | Lactate dehydrogenase |
| LTFU | Long-term follow up |
| LVEF | Left ventricular ejection fraction |
| MCL | Mantle cell lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mEFS | Modified EFS; defined the same way as EFS, except that failure to attain CR or PR by Day 150 assessment is not considered as an event |
| MMSE | Mini-Mental Status Exam |
| MRI | Magnetic resonance imaging |
| MSGV1 | Murine stem cell virus-based vector |
| NCI | National Cancer Institute |
| NE | Neurologic event |
| NHL | Non-Hodgkin lymphoma |
| NMR | No metabolic response |
| NPT | Nasopharyngeal-throat |
| ORR | Objective response rate |
| OS | Overall survival |
| PBMC | Peripheral blood mononuclear cell |
| PCR | Polymerase chain reaction |

| Abbreviation | Definition |
|---|---|
| PD | Progressive disease |
| PET-CT | Positron emission tomography-computed tomography |
| PFS | Progression-free survival |
| PK | Pharmacokinetic |
| PMBCL | Primary mediastinal B-cell lymphoma |
| PMD | Progressive metabolic disease |
| PMR | Partial metabolic response |
| PR | Partial response |
| PRD | Progressive radiologic disease |
| PRO | Patient reported outcome |
| PRR | Partial radiologic response |
| QoL | Quality of life |
| qPCR | Quantitative polymerase chain reaction |
| RCR | Replication-competent retrovirus |
| r/r | Relapsed/refractory |
| SAE | Serious adverse event |
| scFv | Single-chain variable fragment |
| SCT | Stem cell transplant |
| SD | Stable disease |
| SOA | Schedule of assessment |
| SOC | Standard of care |
| SRD | Stable radiologic disease |
| Study Day 0 | Day of randomization |
| SUSAR | Suspected unexpected serious adverse reaction |
| TBI | Total body irradiation |
| TEAE | Treatment-emergent adverse event |
| TFL | Transformed follicular lymphoma |
| TNF | Tumor necrosis factor |
| Treatment day 0 | Defined as the first day that axicabtagene ciloleucel or CD34+ stem cells for ASCT are administered to the subject |
| ULN | Upper limit of normal |
| UTI | Urinary tract infection |
| VAS | Visual analog scale |
| WBC | White blood cell |
| WPAI:GH | Work productivity and activity impairment questionnaire: general health |

# 1. OBJECTIVES

## 1.1. Primary Objective

- To determine if axicabtagene ciloleucel is superior to standard of care (SOC) as measured by event-free survival (EFS), as determined by blinded central review

## 1.2. Secondary Objectives

- To evaluate the effect of axicabtagene ciloleucel compared to SOC on objective response rate (ORR), as determined by blinded central review
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on overall survival (OS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on progression-free survival (PFS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on duration of response (DOR) and duration of complete response among responding subjects, as determined by blinded central review
- To evaluate the safety of axicabtagene ciloleucel compared to SOC
- To evaluate the effect of axicabtagene ciloleucel on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC

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# 2. DISEASE BACKGROUND AND RATIONALE

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes and, to a lesser extent, in T lymphocytes and natural killer cells. NHL is the most prevalent hematological malignancy and is the seventh most common new cancer among men and women, accounting for 4% of all new cancer cases and 3% of cancer-related deaths {Howlader 2015}.

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for approximately 30% to 40% of all cases {Chaganti 2016, Morton 2006, Sehn 2015}. DLBCL comprises a group of lymphoid malignancies composed of large cells with vesicular nuclei, prominent nucleoli, basophilic cytoplasm, and a high proliferation rate {Martelli 2013}. Patients often present with single or multiple rapidly enlarging symptomatic masses, with up to 40% occurring at extranodal sites, particularly the gastrointestinal tract (stomach and ileocecal region). Centroblast- and immunoblast-like cells are the predominant morphology, and these cells typically express the B-cell markers CD19, CD20, CD22, as well as surface immunoglobulin.

## 2.1. Standard First-line Therapy

Since the 1970s, the CHOP chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) had been standard of care first-line therapy. More intensive combinations failed to show additional survival benefit. The current standard of care for first-line treatment is CHOP in combination with an anti-CD20 monoclonal antibody rituximab (R-CHOP, rituximab-based chemoimmunotherapy) {Flowers 2010}. In the seminal study by the Groupe d'Etude des Lymphomes de l'Adulte, first-line R-CHOP was superior to CHOP {Feugier 2005}, with 10-year OS and PFS of 43.5% versus 27.6% and 36.5% versus 20%, respectively {Feugier 2005}. Thus, while more effective than chemotherapy alone, first-line R-CHOP still only results in long-term disease remission in < 40% of subjects. Recently a Phase 3 trial of first-line R-CHOP versus dose-adjusted R-EPOCH demonstrated no difference in EFS or OS between the regimens {Wilson 2016}.

The International Prognostic Index (IPI), which includes age, performance status, lactate dehydrogenase (LDH) level, stage, and extranodal involvement, correlates with outcomes to standard first-line therapy. More recently, prognostic molecular features have been identified. Gene expression profiling has been used to categorize DLBCL into the germinal center B-cell type, and activated B-cell type is associated with worse outcomes. Additionally, double- and triple-hit lymphomas with translocations of MYC and either BCL2 and/or BCL6 have been shown to have a poor prognosis with R-CHOP chemotherapy {Green 2012}.

## 2.2. Standard Second-line Therapy

Patients with DLBCL who relapse after or are refractory to first-line therapy (relapsed/refractory [r/r] DLBCL) have poor prognosis. In the LNH-98.5 trial, approximately 40% of patients relapse after R-CHOP, and 70% of these patients die within the first 2 years after progression despite salvage therapy, with a median OS of 0.7 years after progression {Coiffier 2010}.

Patients with r/r DLBCL have heterogeneous outcomes to second-line therapy. The goal of salvage chemotherapy is to determine chemo-sensitivity prior to proceeding to high-dose therapy-autologous stem cell transplant (HDT-ASCT). The second-line age-adjusted IPI (sAAIPI: LDH, stage, and performance status) can further predict outcome for r/r DLBCL for both chemotherapy-sensitive and all patients {Hamlin 2003}.

Results of the PARMA trial {Philip 1995} demonstrated superior outcome for salvage therapy plus ASCT compared with salvage therapy alone for patients with r/r DLBCL (5-year EFS of 46% vs 12%, and OS of 53% and 32%, respectively), leading to the adoption of second-line chemotherapy plus ASCT as the standard of care. Patients who are unable to undergo ASCT due to comorbidities or chemotherapy insensitive disease have poor long-term outcomes.

Second-line chemotherapy regimens generally consist of non-cross-resistant drugs to first-line R-CHOP. Common regimens include R-GDP, R-DHAP, R-ICE, and R-ESHAP. Institutional preference and adverse event (AE) profile often dictate which treatment regimen is used. No regimen has demonstrated superiority in a randomized trial. The Phase 3 LY12 trial compared GDP to DHAP followed by HDT and ASCT in patients with r/r DLBCL. ORRs (45% vs 44%), EFS (HR = 0.99), and OS (HR = 1.03) were similar between arms although hematologic toxicity was more severe in the DHAP arm {Crump 2014}. In the Phase 3 CORAL trial, patients with r/r DLBCL were randomized to R-ICE versus R-DHAP followed by HDT and ASCT, followed by a second randomization to rituximab maintenance or no maintenance. ORRs (64% vs 63%) and 3 year OS (47% vs 51%) were similar between the two regimens; however, more hematologic toxicity was associated with R-DHAP. Maintenance with rituximab was not shown to be beneficial after ASCT.

Those with chemo-sensitive disease that responds to second-line chemotherapy proceed to HDT and ASCT. HDT-ASCT involves peripheral stem cell collection, myeloablative high-dose chemotherapy with or without total body irradiation (TBI), and stem cell rescue. Although treatment procedures may vary between different regions and institutions, the general process remains consistent. Stem cells are mobilized from the bone marrow to the periphery with G-CSF and then collected by leukapheresis. HDT utilizes a myeloablative conditioning regimen consisting of combination chemotherapy with or without TBI. The choice of regimens varies because no single regimen has demonstrated superiority in a randomized trial; however, chemotherapy-only regimens may have lower rates of secondary myelodysplastic syndrome and acute myeloid leukemia {Barrington 2010, Darrington 1994, Stone 1994}. A common regimen is carmustine (BCNU), etoposide, ara-C, and melphalan (BEAM), which typically is initiated a week prior to stem cell infusion. G-CSF is administered the day following stem cell infusion to support engraftment and reconstitution of the bone marrow, effectively rescuing hematopoiesis and reducing the period of profound neutropenia during which life-threatening infections can occur. The routine use of G-CSF has led to reduction of early transplant-related mortality, but it remains as high as 5% even in experienced institutions.

In the CORAL trial, patients treated with rituximab-based first-line therapy who relapse within 1 year of diagnosis have poor outcomes. The 1-year EFS in this group (approximately 60% of the patients) was below 20% in those who relapse before 1 year compared to 50% in those with relapse after 1 year {Gisselbrecht 2010}. Also, half of the patients did not reach ASCT,

predominantly due to inadequate response to second-line chemotherapy; approximately 84% due to treatment failure and 9.4% due to toxicity. Inadequate response to second-line chemotherapy implies chemo-resistance, and ASCT would not be indicated because of probable inadequate response to high-dose chemotherapy. Their prognosis is poor, with a median OS of about 4.4 months {Van Den Neste 2016}.

The Phase 3 ORCHARRD trial, the largest second-line study in DLBCL with positron emission tomography (PET)-based assessments, demonstrated that patients with primary refractory or early-relapsed disease have poor outcomes {van Imhoff 2017}. Patients were treated with rituximab- or ofatumumab-based salvage DHAP therapy followed by HDT-ASCT in responders based on PET-CT assessment. Those with primary refractory disease or who relapse ≤ 12 months after completion of first-line treatment, representing 70% of patients in the trial, have lower PFS and OS compared to those who relapse > 12 months, with a highly significant hazard ratio of 0.32 (95% confidence interval [CI] 0.24 to 0.44) and 0.4 (95% CI 0.29 to 0.55), respectively. This, along with results from other ASCT studies {Guglielmi 1998} {Vellenga 2008}, highlights that primary refractory or early relapsed disease, regardless as defined as ≤ 12 months from diagnosis, from CR, or from end of first-line treatment, are poor prognostic factors.

Thus, treatment of patients with r/r DLBCL remains challenging. There is a significant unmet need for better therapies in these patients.

### 2.3. Study Rationale

Patients with r/r DLBCL especially primary refractory and early relapse within 1 year after first-line rituximab-based chemoimmunotherapy have poor prognosis even with HDT-ASCT. Because these patients are resistant to chemotherapy, they may benefit from therapies with different mechanisms of action. 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 bi-specific T-cell engagers 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. Chimeric antigen receptor (CAR) engineered T cells may address these issues and are a promising approach for cancer therapy.

Axicabtagene ciloleucel is an engineered autologous T-cell immunotherapy by which a patient's own T cells are collected and subsequently genetically altered to recognize CD19. CD19 is expressed on the cell surface of B-cell malignancies. In ZUMA-1, which investigated the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, axicabtagene ciloleucel significantly improved ORR ($P < 0.0001$). The ORR was 82% with a complete response (CR) rate of 54%. At the primary analysis, 44% of subjects had ongoing responses (39% in CR) (shown in Table 1). Axicabtagene ciloleucel may have an improved efficacy and tolerability in patients with less chemo-refractory disease and lower disease burden. Therefore, axicabtagene ciloleucel will be compared to SOC in patients with r/r DLBCL.

## 2.4. Anti-CD19 Chimeric Antigen Receptor T Cells

### 2.4.1. CD19 and Expression

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

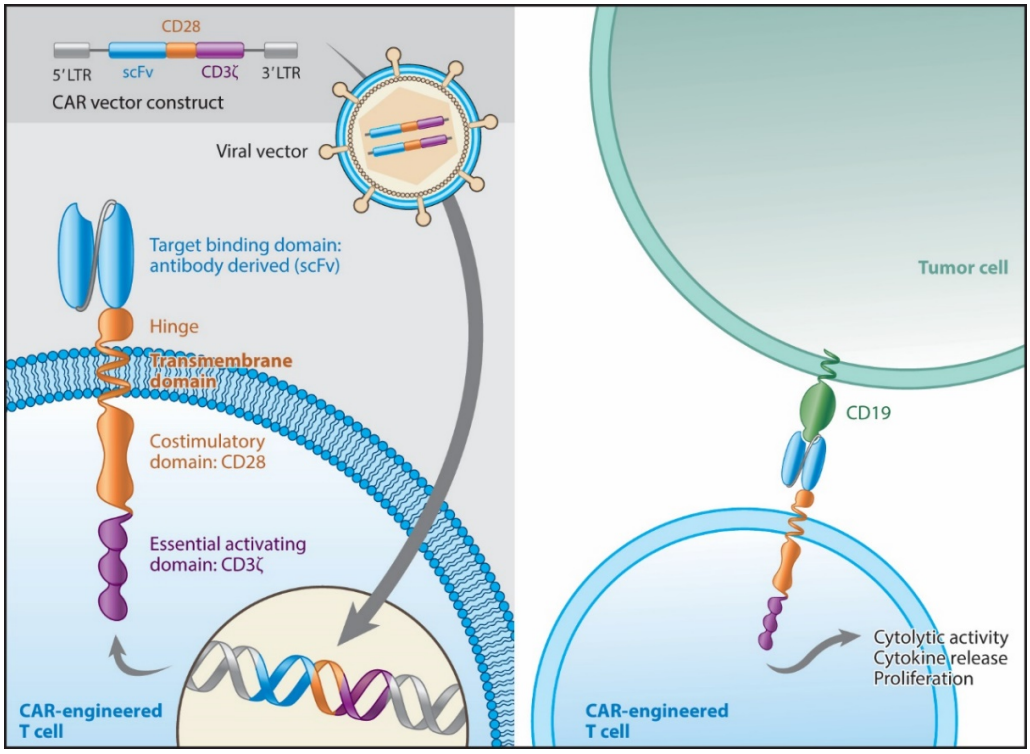
### 2.4.2. Anti-CD19 CAR T-cell Product (Axicabtagene Ciloleucel)

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 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) (refer to Figure 1); {Kochenderfer 2009, Kochenderfer 2010}. The scFv is derived from the variable region of the anti-CD19 monoclonal antibody FMC63 {Nicholson 1997}. A portion of the CD28 costimulatory molecule is added, as murine models suggest this is important for the anti-tumor effect and expansion of anti‑CD19 CAR T cells {Kowolik 2006}. The signaling domain of the CD3ζ chain is essential for T-cell activation. These fragments were cloned into the murine stem cell virus-based vector (MSGV1), utilized to genetically engineer the autologous T cells. The safety and efficacy of anti-CD19 CAR T cells has been evaluated in subjects with CD19+ B-cell malignancies at the NCI {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017}. The same anti‑CD19 CAR vector construct used in the NCI protocol and ZUMA-1 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. PBMCs are activated by culturing with an anti-CD3 antibody in the presence of recombinant human 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 1. Anti-CD19 CAR Construct and Mechanism of Action**




Abbreviations: CD, cluster of differentiation; LTR, long terminal repeat; scFv, single-chain variable fragment; CAR, chimeric antigen receptor.

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

### 2.5.1. ZUMA-1

Kite Pharma, Inc. (hereafter referred to as Kite or Kite Pharma) is developing axicabtagene ciloleucel, which targets CD19 expressing B-cell malignancies. The CAR vector construct is identical to the one used in NCI protocols {Kochenderfer 2017}. Kite Pharma, in conjunction with the NCI Surgery Branch, has developed a streamlined process for the generation of the anti-CD19 CAR T cells. The ZUMA-1 study design and results from the most current interim analysis at the time of protocol development is summarized below.

To review the latest data from the ZUMA-1 study, please refer to the Investigator's Brochure (IB).

#### 2.5.1.1. ZUMA-1 Study Design

ZUMA-1 is phase 1/2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL.

The primary objective of Phase 1 was to evaluate the safety of axicabtagene ciloleucel regimens. The primary objective of Phase 2 was to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate in subjects with DLBCL, PMBCL, and TFL. Secondary objectives included assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints. Phase 2 subjects enrolled into 2 separate cohorts designated as Cohort 1 and Cohort 2. Cohort 1 would enroll approximately 72 adult subjects with refractory DLBCL, and Cohort 2 intended to enroll up to 40 adult subjects with refractory PMBCL and TFL.

Subjects were treated with conditioning chemotherapy consisting of fludarabine 30 $mg/m^2$/day and cyclophosphamide 500 $mg/m^2$/day, administered for 3 days followed by 2 rest days before receiving axicabtagene ciloleucel. Axicabtagene ciloleucel was administered as 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. After investigational product (IP) was dosed, subjects were assessed for post-treatment response followed by a long-term follow-up period for duration of response and overall survival.

#### 2.5.1.2. ZUMA-1 Primary Analysis

As of 27 Jan 2017, the time of the primary analysis data cutoff, 77 subjects in Cohort 1 and 24 subjects in Cohort 2 were evaluable (Table 1). Axicabtagene ciloleucel was successfully manufactured in 99% of subjects enrolled. Average turnaround time from apheresis to receipt of axicabtagene ciloleucel at clinical sites was 17 days.

With an ORR of 82% in Cohort 1+2, the study met the primary endpoint ($P < 0.0001$; exact binomial test comparing observed ORR to historical control of 20%), with 49% CRs. In all 101 subjects, ORR was 82%, with CR in 54% and a median time to CR of 1 month (Table 1); 44% had ongoing responses (CR in 39%) at the time of the primary analysis. ORR was consistent across a broad range of covariates, including refractory subgroup, stage, IPI, and age.

With a median follow-up time of 8.7 months, the median DOR was 8.1 months. The median DOR in subjects achieving CR was not reached. The median PFS was 5.9 months, and the median OS was not reached. Kaplan–Meier estimates of OS at 6, 9, and 12 months were 79.8%, 68.4% and 54.5%.

The most common Grade 3 or higher treatment-emergent AEs (TEAEs) are also shown in Table 1. There were two Grade 5 axicabtagene ciloleucel related events, including hemophagocytic lymphohistiocytosis (HLH) and cardiac arrest in the setting of cytokine release syndrome (CRS).

Peak CAR T-cell expansion was associated with ongoing response at 3 months ($P = 0.004$) and Grade $\geq 3$ neurological events (NEs; $P = 0.02$). Subjects with Grade $\geq 3$ CRS and NEs had increased levels of IL-15 ($P = 0.04$ and $P = 0.006$, respectively) and IL-6 ($P = 0.001$ and $P = 0.0003$, respectively).

**Table 1. Baseline Characteristics and Results from ZUMA-1 Primary Analysis**

| | Cohort 1 DLBCL (N = 77) | Cohort 2 PMBCL/TFL (N = 24) | Total (N = 101) |
|---|---|---|---|
| Baseline Characteristics | | | |
| Median Age (range), years | 58 (25-76) | 57 (23-76) | 58 (23-76) |
| Age ≥ 65 years, n (%) | 17 (22) | 7 (29) | 24 (24) |
| Male, n (%) | 50 (65) | 18 (75) | 68 (67) |
| ECOG performance status 1, n (%) | 49 (64) | 10 (42) | 59 (58) |
| Received ≥ 3 lines of prior therapy | 49 (64) | 21 (88) | 70 (70) |
| Refractory ≥ 2 lines of prior therapy | 59 (77) | 19 (79) | 78 (77) |
| Relapse post ASCT | 16 (21) | 5 (21) | 21 (21) |
| Response | | | |
| Objective response rate, n (%) | 63 (82) | 20 (83) | 83 (82) |
| 95% CI<br>P-value[a] | (71, 90) | (63, 95) | (73, 89)<br>P<0.0001 |
| Best response, n (%) | | | |
| CR | 38 (49) | 17 (71) | 55 (54) |
| PR | 25 (32) | 3 (13) | 28 (28) |
| Safety | Total (N=101) | | |
| Common Grade 3 or higher AEs, n (%)[b] | | | |
| Neutropenia/neutrophil count decreased | 66 (66) | | |
| Leukopenia/WBC count decreased | 44 (44) | | |
| Anemia | 43 (43) | | |
| Febrile neutropenia | 31 (31) | | |
| Thrombocytopenia | 24 (24) | | |
| Encephalopathy | 21 (21) | | |
| Grade 3 or higher AEs of clinical interest, n (%) | | | |
| Cytokine release syndrome[c] | 13 (13) | | |
| Neurological events[c] | 28 (28) | | |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; PR, partial response; AE, adverse event; WBC, white blood count.
Notes: All AEs are treatment emergent.
a Exact binomial test comparing observed ORR in DLBCL to a historical control assumption of 20%.
b Occurring in > 20% of patients.
c Combined terms.

### 2.5.2. CAR T-cell Receptor Immunotherapy for Patients with B-cell Lymphoma (Protocol 09-C-0082, NCT00924326)

The NCI clinical study (Protocol 09-C-0082) of anti-CD19 CAR T-cell therapy has demonstrated durable objective responses in patients with advanced B-cell malignancies, including NHL. This study enrolled adults age 18 to 68 with B-cell lymphomas or leukemias expressing CD19 as cohorts to determine the safety and feasibility of the administration of anti-CD19-CAR engineered peripheral blood lymphocytes with a nonmyeloablative conditioning regimen. The CAR construct is identical to the one used in ZUMA-1. In the NCI cohort of 43 subjects with relapsed/refractory B-cell malignancies, the ORR was 74%, with a CR rate of 54% and a partial response (PR) rate of 21% (as of 10 Nov 2016, data on file at Kite Pharma). Twenty-one of the 43 subjects (49%) were still in response, with a median follow-up of 36 months (range 13 to 78 months). Median DOR was 35 months (range 23 to 77 months). Nineteen subjects (44%) had ongoing responses for more than 1 year. Median PFS and OS have not been reached.

In the most recent report focusing on 22 subjects treated with low dose conditioning chemotherapy, 19 had DLBCL, 2 had follicular lymphoma (FL), and one had MCL {Kochenderfer 2017}. The CR rate was 55% and PR rate was 18%. In particular, among a subset of 19 subjects with DLBCL, the ORR was 68% with a CR in 47% and a PR in 21%. Of the 12 subjects who achieved CR, 11 remain in CR, with a median duration of 12.5 months and longest of 24 months ongoing at the time of analysis. PFS was 63.6% at 12 months. Remissions were associated with high serum IL-15 levels and high peak blood CAR T-cell expansion. Reversible Grade 3 or 4 neurologic toxicities were observed in 55% of subjects, with no Grade 5 events. Complete resolution was observed within the majority of subjects with supportive treatment; only 1 subject received dexamethasone and 2 received tocilizumab. Neurologic toxicity was associated with high peak blood CAR T-cell levels and high serum granzyme B, IL-10, and IL-15 levels.

# 3. STUDY DESIGN

## 3.1. General Study Design: ZUMA-7

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOC in adult subjects with r/r DLBCL. Adult subjects with r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOC. Randomization will be stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1 vs 2 to 3) as assessed at the time of screening.

For subjects randomized to the control arm of the study, SOC will consist of a protocol-defined, platinum-based salvage combination chemotherapy regimen. Subjects who respond to second-line chemotherapy should proceed to HDT and ASCT.

An independent Data Safety Monitoring Board (DSMB) will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed. Refer to Section 9.9 for further details.

For study requirements assigned to each study arm, please refer to the schedule of assessments (SOAs) 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 80 centers located in North America, Europe, and Israel will participate in this study. During the conduct of the study, additional sites, regions, or countries 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 350 subjects will be randomized into this study.

## 3.4. Replacement of Subjects

Subjects will not be replaced, and all subjects randomized will be included in the intent-to-treat analysis.

## 3.5. Duration of Study and Subject Participation

### 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 study will take approximately 5 years to complete for those randomized to the SOC arm and approximately 15 years to complete for those randomized to the axicabtagene ciloleucel arm. Individual study duration may vary depending on a subject's screening requirements, response to treatment, potential for re-treatment, survival and timing of transition to a separate Kite Long-term Follow-up (LTFU) study (discussed in Section 3.5.3 and Section 7.15).

The need for prolonged follow-up is based on the potential presence of replication-competent retrovirus (RCR) in treated subjects and the need to understand and mitigate the potential risks of delayed onset AEs that could be the potential consequence of treatment with this emerging technology.

### 3.5.2. End-of-study Definition

The end of study is defined as when the last remaining subject completes their last visit on this study and transitions to a separate LTFU study (Section 3.5.3), or, when the last remaining subject, while still a participant in this study, is considered lost to follow-up, withdraws full consent, or dies.

### 3.5.3. Long-term Follow-up

After completing at least 60 months of assessments in this study, all subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will be transitioned to a separate LTFU study after providing informed consent, where they will be monitored for the possible occurrence of late-onset targeted AEs/serious AEs (SAEs) including secondary malignancies, and the presence of RCR suspected to be related to axicabtagene ciloleucel for up to 15 years (refer also to Section 7.15). In the LTFU study, subjects will continue assessments at timepoints contiguous with their timepoint in this study.

# 4. SUBJECT SCREENING AND ENROLLMENT

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

Kite Pharma will assign a unique 9-digit screening subject identification (ID) number before any study procedures are performed for all subjects who enter into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) as described in the Investigational Product Manual (IPM). This screening subject identification 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 screening subject identification number will remain constant throughout the entire clinical study; it will not be changed after enrollment or if the subject is rescreened or retreated.

Following all screening activities, the subject will be registered in the Interactive Voice/Web Response System (IXRS) for randomization upon the investigator confirming eligibility of the subject. For further details on the consent, screening, and enrollment process, refer to Section 7, the IPM, and the IXRS manual.

# 5. SUBJECT ELIGIBILITY

## 5.1. Inclusion Criteria

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

- DLBCL not otherwise specified (including ABC/GCB)
- HGBL with or without MYC and BCL2 and/or BCL6 rearrangement
- DLBCL arising from FL
- T-cell/histiocyte rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Primary cutaneous DLBCL, leg type
- Epstein-Barr virus (EBV) + DLBCL

102) Relapsed or refractory disease after first-line chemoimmunotherapy

- Refractory disease defined as no complete remission to first-line therapy; subjects who are intolerant to first-line therapy 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 (eg, 4 cycles of R-CHOP)
  - PR as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy
- Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven disease relapse ≤ 12 months of first-line therapy

103) Subjects must have received adequate first-line therapy including at a minimum:

- Anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and
- An anthracycline containing chemotherapy regimen

104) Intent to proceed to HDT and ASCT if response to second-line therapy

105) Subjects must have radiographically documented disease

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

107) At least 2 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the subject provides consent

108) Age 18 years or older at the time of informed consent

109) ECOG performance status of 0 or 1

110) Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:

- Absolute neutrophil count (ANC) ≥1000/μL
- Platelet count ≥ 75,000/μL
- Absolute lymphocyte count ≥ 100/μL
- Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min
- Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dl, except in subjects with Gilbert's syndrome
- Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings
- No clinically significant pleural effusion
- Baseline oxygen saturation > 92% on room air

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

### 5.2. Exclusion Criteria

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

202) History of Richter's transformation of CLL or PMBCL

203) History of autologous or allogeneic stem cell transplant

204) Received more than one line of therapy for DLBCL

205) Prior CD19 targeted therapy

206) Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 6 weeks or 5 half-lives of the drug, whichever is shorter, prior to the first dose of axicabtagene ciloleucel or SOC

207) Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy or prior randomization into ZUMA-7

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

209) Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment.

210) Known history of infection with human immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing.

211) Active tuberculosis

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

213) Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases or with a history of cerebrospinal fluid malignant cells or brain metastases

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

215) Subjects with cardiac atrial or cardiac ventricular lymphoma involvement

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

217) Requirement for urgent therapy due to tumor mass effects, such as bowel obstruction or blood vessel compression

218) History of autoimmune disease requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years

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

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

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

222) History of severe immediate hypersensitivity reaction to tocilizumab or any of the agents used in this study (for sites in Switzerland, refer to the additional country-specific exclusion criterion in Appendix D)

223) Treatment with a live, attenuated vaccine within 6 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the course of the study

224) Women of childbearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of chemotherapy on the fetus or infant. Subjects of either sex who are not willing to practice birth control from the time of consent and at least 6 months after the last dose of axicabtagene ciloleucel or SOC chemotherapy

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

# 6. PROTOCOL TREATMENT

## 6.1. Treatment Terminology

For subjects randomized to the axicabtagene ciloleucel arm of the study:

- Bridging therapy refers to corticosteroids administered after leukapheresis through 5 days prior to administration of axicabtagene ciloleucel.
- Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of axicabtagene ciloleucel.
- The investigational product is named axicabtagene ciloleucel.

For subjects randomized to the SOC arm of the study:

- The second-line combination chemotherapy regimen refers to the rituximab and platinum-based chemotherapy regimen.
- The second-line combination chemotherapy regimen will be selected by the treating investigator. The allowed regimens are R-ICE, R-DHAP, R-ESHAP, or R-GDP.
- Response to second-line combination chemotherapy refers to a PR or CR after 2 or 3 cycles.
- Stem cell collection refers to CD34+ hematopoietic stem cells collected by leukapheresis from the peripheral blood after G-CSF stimulation.

HDT refers to the myeloablative regimen administered prior to autologous stem cell infusion. The HDT regimen will be selected by the treating investigator.

For subjects randomized to either the axicabtagene ciloleucel or the SOC arm of the study:

- Leukapheresis refers to:
  - The procedure for collection of peripheral blood mononuclear cells used to manufacture the subject-specific axicabtagene ciloleucel treatment (axicabtagene ciloleucel arm) or
  - The procedure for peripheral CD34+ hematopoietic stem cell collection (SOC arm). Cells collected with the intent of ASCT will follow institutional guidelines and will not be shipped to Kite Pharma.
- Concomitant medication refers to treatment that subjects can receive during the conduct of the study.
- Excluded medications refer to treatment that is not to be administered, unless otherwise specified, during the conduct of the study.

Subsequent new lymphoma therapy refers to treatment administered after axicabtagene ciloleucel or SOC necessary to treat a subject's disease.

## 6.2. Axicabtagene Ciloleucel Study Treatment Arm

### 6.2.1. Leukapheresis

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of axicabtagene ciloleucel. Leukapheresed cells obtained at participating centers will be shipped to the Kite manufacturing facility as described in the IPM.

### 6.2.2. Conditioning Chemotherapy

Conditioning chemotherapy for lymphodepletion will be supplied by the investigative site unless otherwise noted. Treatment should be administered per institutional guidelines. Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

#### 6.2.2.1. 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.

#### 6.2.2.2. Cyclophosphamide

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

#### 6.2.2.3. Mesna

Mesna is a detoxifying agent used to prevent 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 $C_2H_5NaO_3S_2$.

#### 6.2.2.4. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy {Dudley 2008}. Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in pre-clinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8+ T cells {Gattinoni 2005}. Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation {Klebanoff 2005}. Cyclophosphamide and fludarabine combination is a potent lymphodepleting regimen. Cyclophosphamide (500 mg/m$^2$/day) and fludarabine (30 mg/m$^2$/day) both given for

3 consecutive days has been studied and tolerated in subjects with B-cell malignancies {O'Brien 2001} and was used in the ZUMA-1 trial {Locke 2017}.

### 6.2.3. Axicabtagene Ciloleucel

#### 6.2.3.1. Investigational Product Description

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

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

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

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

#### 6.2.3.2. Rationale for Axicabtagene Ciloleucel Dose

The rationale for the axicabtagene ciloleucel dose in this study is based on the aggregate safety and efficacy data compiled from the ZUMA-1 study as outlined in Section 2.5.1.2 and the IB. Based on the favorable benefit/risk ratio seen in ZUMA-1, axicabtagene ciloleucel will be administered at a target dose of $2 \times 10^6$ anti-CD19 CAR T cells/kg, but may be dosed at a minimum of $1 \times 10^6$ anti-CD19 CAR T cells/kg. For subjects weighing > 100 kg, a maximum flat dose of axicabtagene ciloleucel at $2 \times 10^8$ anti-CD19 CAR T cells will be administered.

### 6.2.4. Cell Collection and Axicabtagene Ciloleucel Study Treatment Schedule and Administration

#### 6.2.4.1. Leukapheresis (Within Approximately 5 Days of Randomization)

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

Before leukapheresis commences, the below criteria must be met:

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

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

The leukapheresis visit should occur within approximately 5 days of randomization.

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

Refer to the SOA Table 2 for a listing of study procedures to be completed during the leukapheresis visit.

#### 6.2.4.2. Bridging Therapy (administered after leukapheresis and completed at least 5 days prior to initiating axicabtagene ciloleucel)

At the discretion of the investigator, bridging therapy may be considered for subjects with high disease burden at screening.

Bridging therapy with corticosteroids is allowed, such as dexamethasone at a dose of 20 to 40 mg or equivalent, either PO or IV daily for 1 to 4 days. Choice of corticosteroid and dosing can be adjusted for age/comorbidities or per clinical judgement.

#### 6.2.4.3. Conditioning Chemotherapy (day -5 through day -3 before infusion of axicabtagene ciloleucel)

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

Signs, symptoms, or abnormal laboratory results attributed to the malignancy (eg "tumor fever," elevated C-reactive protein [CRP]) are diagnoses of exclusion that require a documented work-up to establish.

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

Refer to Section 6.2.4.8 for Requirements to Work-up Potential Infectious and/or Inflammatory States.

##### 6.2.4.3.1. Requirements for Initiation of Conditioning Chemotherapy

If any of the following criteria are met prior to the initiation of conditioning chemotherapy, then the work-up listed in Section 6.2.4.8 must be performed to determine the potential cause if there is no identified source of infection.

- Temperature > 38°C within 72 hours of conditioning chemotherapy
- CRP > 100 mg/L anytime between enrollment to start of conditioning chemotherapy
- White blood cell (WBC) count or WBC differential concerning for infectious process between enrollment to start of conditioning chemotherapy (eg, WBC > 20,000, rapidly increasing WBC, or differential with high percentage of segs/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, throat (HEENT); cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before conditioning chemotherapy (prophylactic use of anti-microbials 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 work-up 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.

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

#### 6.2.4.3.2. Conditioning Chemotherapy Administration (day -5 through day -3 Prior to Axicabtagene Ciloleucel Infusion)

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

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

- IV hydration with a balanced crystalloid according to institutional guidelines prior to administration of cyclophosphamide on the day of infusion

- Cyclophosphamide 500mg/$m^2$ IV over approximately 60 minutes

- Fludarabine 30mg/$m^2$ IV over approximately 30 minutes

- Additional IV hydration with a balanced crystalloid according to institutional guidelines to be administered upon completion of the cyclophosphamide infusion

- Mesna to be administered per institutional guidelines

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

Refer to the SOA Table 2 for a listing of study procedures to be completed during the axicabtagene ciloleucel conditioning chemotherapy period.

#### 6.2.4.4. Requirements for Initiating Axicabtagene Ciloleucel Infusion (Treatment day 0)

If any of the following criteria are met prior to the initiation of axicabtagene ciloleucel infusion, then the work-up listed in Section 6.2.4.8 must be performed to determine the potential cause if there is no identified source of infection.

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

Additionally:

- If any screening assessments or procedures are repeated between confirmation of eligibility and the start of axicabtagene ciloleucel infusion and results are outside the eligibility criteria listed in Section 5, then the condition must resolve prior to proceeding with axicabtagene ciloleucel infusion (except for peripheral blood cell counts that have been impacted by conditioning chemotherapy).
- Complete history and physical exam including HEENT; cardiac, vascular, respiratory, gastrointestinal, integumentary, and neurological systems must not reveal evidence of infection/inflammation.
- The subject must not have received systemic anti-microbials for the treatment of a known or suspected infection within 48 hours before axicabtagene ciloleucel (prophylactic use of anti-microbials 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 work-up 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.

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

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

#### 6.2.4.5. Axicabtagene Ciloleucel Premedication Dosing

The following pre axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion.

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

#### 6.2.4.6. Axicabtagene Ciloleucel Administration day 0

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

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

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

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

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of axicabtagene ciloleucel. Catheter care, per institutional guidelines, should be followed. Materials and instructions for the thawing, timing, and administration of axicabtagene ciloleucel are outlined in the IPM. Vital signs should be measured during and after axicabtagene ciloleucel treatment (see Section 7.6). The IPM must be reviewed prior to administration of axicabtagene ciloleucel.

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

#### 6.2.4.7. Axicabtagene Ciloleucel Retreatment

Subjects who achieved a PR or CR and subsequently experience disease progression may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel.

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

- Subject had a PR or CR at the first disease assessment at Day 50 but subsequently experienced progression of disease at a later time
- Tumor that is not known to be CD19 negative
- Subject continues to meet the original study eligibility criteria with the exception of prior axicabtagene ciloleucel use in this study; screening assessments and procedures should be repeated if clinically indicated (eg, magnetic resonance imaging [MRI], ECHO)
- Subject has not received subsequent therapy for the treatment of lymphoma
- Subject did not experience a life-threatening toxicity related to axicabtagene ciloleucel during the original course of treatment
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to re-treatment
- Subject does not have known axicabtagene ciloleucel neutralizing antibodies (exception: if a non-neutralizing axicabtagene ciloleucel antibody develops, subjects may be retreated if they meet the original study eligibility criteria)
- Sites are strongly encouraged to collect a biopsy confirming disease progression and CD19 expression and to submit the biopsied tissue to the central laboratory before initiating re-treatment
- Subject received the initial axicabtagene ciloleucel infusion ≤ 24 months ago

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

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

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

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

Refer to the SOA Table 2 for a listing of study procedures to be completed during the axicabtagene ciloleucel treatment period.

#### 6.2.4.8. Requirements to Work-up Potential Infectious and/or Inflammatory States

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

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

- If a central nervous system process is suspected, appropriate brain imaging and subsequent lumbar puncture with cytology, culture, Gram stain, and viral PCR should be performed.

- Any additional sign or symptom-directed investigation should be performed as clinically indicated.

Prior to proceeding with conditioning chemotherapy and/or axicabtagene ciloleucel infusion, the above work-up 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 work-up was triggered due to CRP > 100 mg/L, CRP should be repeated, and if CRP continues to increase significantly, evaluation should be performed for any other potential infectious or inflammatory condition not previously evaluated.

#### 6.2.4.9. Concomitant Therapy (Axicabtagene Ciloleucel Arm)

Investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis except those medications listed in the excluded medication Section 6.2.5. Concomitant therapy does not include therapy used for the treatment of the disease.

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

For subjects who are randomized but not dosed with axicabtagene ciloleucel, concomitant concurrent therapies and subsequent anticancer therapy will only be recorded from the date of the informed consent through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy).

For subjects who are randomized to receive axicabtagene ciloleucel and receive the dose of axicabtagene ciloleucel, all concomitant therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent through the Day 150 post-randomization visit, and targeted concomitant therapies from this visit until Month 12, or until a change in lymphoma therapy, or disease progression, whichever occurs first. Targeted concomitant therapies include gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations. Refer to Section 6.2.6 for details surrounding subsequent cancer therapy.

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

### 6.2.5. Excluded Medications (Axicabtagene Ciloleucel Arm)

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

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

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

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

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

### 6.2.6. Subsequent Therapy (Axicabtagene Ciloleucel Arm)

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

### 6.2.7. Toxicity Management (Axicabtagene Ciloleucel Arm)

To date, the following important risks have been identified with axicabtagene ciloleucel: CRS, neurologic events, infections, cytopenias, and hypogammaglobulinemia. 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.

## 6.3. Standard of Care Therapy Arm

SOC therapy will be supplied by the investigative site unless otherwise noted. Refer to the current product label for guidance on packaging, storage, preparation, and administration of each chemotherapy regimen and individual component of the regimen. G-CSF will be administered based on regional/institutional standards to prevent chemotherapy delays and infection and for leukapheresis.

Administration of SOC therapy will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Any overdose or incorrect administration of SOC therapy should be noted on the Study Drug Administration electronic Case Report Form (eCRF).

After SOC therapy is administered to a subject, the subject must receive the same SOC therapy option for subsequent cycles of therapy. Individual agents of the choice of treatment may be altered based on subject care and toxicity management.

### 6.3.1. Standard of Care Chemotherapy Dosing and Administration

SOC chemotherapy is recommended to start within approximately 5 days after randomization.

Rituximab + ifosfamide, carboplatin, and etoposide (R-ICE) suggested dosing {Gisselbrecht 2010}:

- Rituximab 375 mg/m$^2$ before chemotherapy
- Ifosfamide 5 g/m$^2$ 24h-CI on day 2 with mesna
- Carboplatin area under the curve (AUC) 5 on day 2, maximum dose 800 mg
- Etoposide 100 mg/m$^2$/d on days 1-3

Rituximab + etoposide, methylprednisolone, cytarabine, cisplatin (R-ESHAP) suggested dosing {Martin 2008}:

- Rituximab 375 mg/m$^2$ day 1
- Etoposide 40 mg/m$^2$/d IV on days 1-4
- Methylprednisolone 500 mg/d IV on days 1-4 or 5
- Cisplatin at 25 mg/m$^2$/d CI days 1-4
- Cytarabine 2 g/m$^2$ on day 5

Rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin (R-GDP) suggested dosing {Crump 2004, Gopal 2010}

- Rituximab 375 mg/m$^2$ day 1 (or day 8)
- Gemcitabine 1 g/m$^2$ on days 1 and 8
- Dexamethasone 40 mg on days 1-4
- Cisplatin 75 mg/m$^2$ on day 1 (or carboplatin AUC = 5) {Gopal 2010}

Rituximab + dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) suggested dosing {Gisselbrecht 2010}:

- Rituximab 375 mg/m$^2$ before chemotherapy
- Dexamethasone 40 mg/d on days 1-4
- High-dose cytarabine 2 g/m$^2$ every 12 h for 2 doses on day 2 following platinum
- Cisplatin 100 mg/m$^2$ 24h-CI on day 1 (or oxaliplatin 100 mg/m$^2$) {Lignon 2010}

#### 6.3.1.1. Rationale for Standard of Care Dose and Schedule

Second-line chemotherapy regimens generally consist of non-cross-resistant drugs to first-line R-CHOP and includes platinum. Common regimens include R-GDP, R-DHAP, R-ICE, and R-ESHAP. Institutional preference and toxicity profile often dictate which treatment regimen is used because no single salvage regimen has demonstrated superiority in a randomized trial. If adequate disease response (CR or PR) is demonstrated after 2 or 3 cycles of chemotherapy, HDT-ASCT may be initiated.

Prior to high-dose therapy, which is myeloablative, peripheral blood progenitor cells are collected by leukapheresis to a minimum target of 2 x 10$^6$ CD34+ hematopoietic stem cells per kg body weight, which will be reinfused after HDT to rescue hematopoiesis. The HDT conditioning regimen consists of combination high-dose chemotherapy with or without TBI. Commonly used high-dose regimens include BEAM (BCNU, etoposide, ara-C, and melphalan) or CBV (cyclophosphamide, BCNU, and VP-16). There is no standard high-dose regimen due to lack of randomized studies; therefore, HDT and ASCT procedures are per regional and institutional standards.

### 6.3.2. Concomitant Therapy (Standard of Care Arm)

Investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis, except those medications listed in the excluded medication Section 6.3.3. Concomitant therapy does not include therapy used for the treatment of the disease.

For subjects who are not randomized (eg, screen failure), only concurrent therapies related to any SAEs will be recorded.

For subjects who are randomized but not dosed with SOC, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study-specific procedure.

For subjects who are randomized and receive SOC therapy, all concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded from the date of the informed consent through the Day 150 post-randomization visit or disease progression, whichever occurs first. Refer to Section 6.3.4 for details surrounding subsequent cancer therapy.

Specific concomitant medication collection requirements and instructions are included in the CRF completion guidelines.

### 6.3.3. Excluded Medications (Standard of Care Arm)

Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation (TBI for HDT is allowed), and high-dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited, except as needed for change in lymphoma therapy after lack of response to the protocol-defined SOC therapy options.

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

### 6.3.4. Subsequent Therapy (Standard of Care Arm)

Subsequent therapy administered after SOC chemotherapy necessary to treat a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, as well as stem cell transplant and radiation therapy, will be recorded for all subjects randomized until the subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies. If a subject progresses, sites are strongly encouraged to collect a biopsy confirming disease progression and to submit the biopsied tissue to the central laboratory.

### 6.3.5. Toxicity Management (Standard of Care Arm)

Refer to the current regional product label, and follow institutional guidelines for toxicity management associated with the administration of each chemotherapy agent.

# 7. STUDY PROCEDURES

Research staff should refer to the SOAs for an outline of the procedures required.

The visit schedule for disease assessments, including CT scans, positron emission tomography (PET) scans, bone marrow biopsy, assessment of B-symptoms, physical exams needed to assess disease, and collection of subsequent new lymphoma therapy, is calculated from randomization.

An overview of study assessments/procedures is outlined below. Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

## 7.1. Informed Consent

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

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

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

## 7.2. Screening

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

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

After written informed consent has been obtained, Kite Pharma will assign a screening number to the subject. Subsequently, the subject will be registered into the IXRS as described in the IXRS user manual. Subjects who fail to meet the eligibility criteria will be allowed to rescreen

one time. Subjects will perform the assessment that initially resulted in the subject failing screening, including any other procedures that fell outside of the designated screening window (ie, lab assessments or PET-CT scans).

Only subjects who meet the eligibility criteria listed in Section 5 will be randomized into the study. If at any time prior to enrollment the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure in the IXRS and on the subject screening log with the reasons for failing screening.

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

### 7.3. Randomization

Once eligibility into the study has been confirmed, subjects will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or investigator choice of SOC chemotherapy as assigned by the IXRS.

To randomize a subject, an authorized site representative will log into IXRS where the system will assign a randomization number to the subject. The randomization is accomplished by entering the pertinent information detailed in the IXRS user manual. Randomization will be stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1 vs 2 to 3) as assessed at the time of screening.

After data have been entered into the IXRS, a confirmation fax or email will be sent to the site to verify that the correct information has been entered. The site representative will receive a single, unique randomization number for each subject and the randomization treatment assigned. A subject will be considered enrolled/randomized into the study when a randomization number is assigned.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

Depending on which arm of the study subjects are randomized, subjects should initiate leukapheresis or SOC therapy within approximately 5 days of randomization in IXRS.

### 7.4. Demographic Data

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

### 7.5. 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 subject's chart should be obtained.

### 7.6. Physical Exam, Vital Signs, and Performance Status

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.

Vital signs, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, will be monitored and recorded at times outlined in the SOA.

In addition to the time points outlined in the SOA, it is recommended that vital signs be monitored during and after axicabtagene ciloleucel or SOC therapy and every 6 hours during any hospitalization. Vital signs may be monitored more frequently as clinically indicated.

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

### 7.7. Neurological Examination

A neurological examination will be performed with any abnormalities of the following recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). A neurological assessment (which may include the Mini-Mental Status Exam [MMSE]) should be done prior to axicabtagene ciloleucel infusion on treatment day 0, then on treatment day 1, and every other day during the minimum 7-day observation period (refer to Appendix D for specific requirements of country regulatory agencies regarding duration of observation period).

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

### 7.8. Cardiac Function

Each subject's cardiac function, as measured by left ventricular ejection fraction (LVEF), will be assessed during the screening period to confirm study eligibility. No evidence of pericardial effusion as required by eligibility will also be confirmed. Both LVEF and pericardial effusion will be assessed prior to study entrance by ECHO. An ECHO performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

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

## 7.9. Toxicity Evaluation

Specific to subjects who are randomized into the axicabtagene ciloleucel arm of the study and receive axicabtagene ciloleucel as part of their initial treatment, or as part of re-treatment, suspected related toxicities should be evaluated with the following:

- For new onset symptoms potentially related to CRS, a physical exam, and assessments of vital signs (including pulse oximetry) and cardiopulmonary status should be performed. Refer to the SOA Table 2 for further details, Section 6.2.7, and the IB for CRS management.

- For new onset neurologic symptoms, neurologic assessment should be performed at least daily until symptoms resolve to baseline. For Grade ≥ 2 neurological symptoms, a brain MRI, electroencephalogram (EEG), and examination of CSF should be performed in addition to frequent neurologic assessment. Additional evaluations of the CSF should be performed per institutional standard of care. CSF samples (ie, if collected at baseline, and collected on study to assess neurological symptoms) will be submitted to the central laboratory. Refer to the SOA Table 2 for further details, Section 6.2.7, and the IB for management.

- For Grade ≥ 3 CRS, neurologic, or HLH symptoms, CRP and ferritin levels should be evaluated and followed.

## 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 Lugano Classification {Cheson 2014}. Flow cytometric, molecular, or cytogenetic studies will not be used to determine response.

### 7.10.1. Imaging

Screening fluorodeoxyglucose (FDG)-PET from skull base to mid-thighs and diagnostic quality contrast-enhanced (unless contraindicated) CT from skull base through lesser trochanters (PET-CT), along with the appropriate imaging of all other sites of disease, are required to confirm eligibility and to establish a baseline, which must be performed within 28 days prior to randomization and as close to the randomization date as possible. Subjects will have their first post-treatment planned PET-CT tumor assessment within the Day 50 assessment period calculated from the subject's randomization date.

Subjects' disease will further be assessed and at regular intervals as highlighted in the SOA during the post treatment and long-term follow-up portion of the study. PET-CTs will continue through Month 9 or until change in lymphoma therapy or disease progression, whichever comes first. If subject's disease has not progressed by Month 9, disease assessments can be evaluated per CT scans where a CR is suspected and per PET-CTs where a PR is suspected. Subjects with symptoms suggestive of disease progression should be evaluated for progression at the time symptoms occur even if it is off schedule as per the SOA. PET-CT can be performed at any time disease progression is suspected. FDG-PET assessment takes precedence over CT assessment for time points when both are available. If only CT is available for a time point, assessment should include and may be affected by the PET-CT assessment at the prior time point. Please refer to the imaging manual for further details.

In addition to the investigator's assessment, PET-CT scans of all subjects evaluated for disease response will be submitted to and reviewed by an independent central reviewer blinded to treatment arm. For subjects who discontinue protocol therapy due to an assessment of progressive disease but for whom there was no change in lymphoma therapy, any additional imaging data, subsequent to the image in question, will be submitted to the central reviewer to confirm disease response. Requirements for PET-CT scans and shipping requirements will be outlined in the study imaging manual.

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.

### 7.10.2. Bone Marrow Biopsy and Aspirate

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

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

## 7.11. Laboratory

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

### 7.11.1. Local Lab Analysis

- Sodium (Na), potassium (K), chloride (Cl), bicarbonate ($CO_2$), creatinine, glucose, albumin, calcium total, magnesium total (Mg), alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, analyzed per the SOA

- Baseline LDH at screening from a non-hemolyzed sample to be used for the assessment of the sAAIPI

- CRP at leukapheresis, treatment day 0, treatment days 1-7, and for Grade ≥ 3 CRS, neurologic, HLH events.

- Ferritin at leukapheresis, treatment day 0, treatment days 1-7, and for Grade ≥ 3 CRS, neurologic, HLH events.

- CBC with differential analyzed per the SOA

- 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.

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

### 7.11.2. Central Lab Analysis

- Blood draws for levels of anti-CD19 CAR T cells by quantitative polymerase chain reaction (qPCR) analysis and monitoring of lymphocytes subsets, including return of normal B cells, will be performed at intervals outlined in the SOA.

- Blood draws for replication-competent retrovirus (RCR), treatment-related antibody development, and cytokines will be performed at intervals outlined in the SOA or as clinically indicated.

- Archived tumor samples will be submitted to central laboratory for evaluation of CD19 expression and prognostic variables. Either formalin-fixed paraffin-embedded (FFPE) tumor block or 30 unstained slides are required. Should an archived tumor sample not be available, a fresh tumor sample is required prior to initiation of chemotherapy to continue on study. Slides that have been previously stained with antibodies or other reagents are not acceptable.

- Additional analysis may include CD19 expression, gene expression profiling, and analysis of tumor-specific DNA alterations. CCI [redacted]

#### 7.11.2.1. Product Characteristics

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

#### 7.11.2.2. RCR Testing

Axicabtagene ciloleucel comprises T cells transduced with a γ-retroviral vector; hence, there is a theoretical risk for RCR developing in exposed subjects. Additional information is provided in the Investigator's Brochure. The timing of blood draws for determination of the presence of RCR is specified in the SOA or may be done or as clinically indicated.

RCR testing will occur at baseline, study Day 150 and Month 12. Thereafter, samples will be collected yearly until transition to the LTFU study and held for up to 15 years. If a subject tests positive for RCR at any time point within the first year, samples will continue to be collected and tested yearly for up to 15 years or as clinically indicated.

### 7.12. Patient Reported Outcomes

All PROs described below will be completed by the subject before any procedures are performed, excluding blood draws, and at the time points noted in the SOA.

The sponsor will provide training for relevant personnel (eg, key investigators) for the administration of the questionnaires so that subjects fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection {Fallowfield 1987}. The measures are self-reported, and the subject must complete the questionnaires in private and should not be given help from relatives or clinic staff; help in interpreting the questions is not allowed.

Below is a description of each patient reported outcome, which are expected from all subjects who remain on-study at the scheduled assessments. All PRO measures will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual.

#### 7.12.1. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 Version 3.0.

This measure provides a multi-dimensional assessment of health-related quality of life (HRQoL). The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Cancer (QLQ-C30 version 3.0 includes the following content:

- Five (5) multi-item functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning)
- Three (3) multi-item symptom scales (fatigue, nausea and vomiting, pain)
- Six (6) symptom single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties)
- One (1) Global Health Status scale and
- One (1) Global HRQoL scale

Each scale is measured from 0 to 100 after a linear transformation. Higher scores for functioning scales and for the Global Health Status or Global HRQoL scales indicate a higher level of functioning and a better HRQoL respectively, whereas higher scores in symptom scales represent a higher level of symptoms.

This instrument does not sum together all items that can potentially group differences and allows an assessment of change across the 15 different domains. In its current version (version 3), the questionnaire takes approximately 11 minutes to complete.

### 7.12.2. EuroQol Five Dimensions Questionnaire (EQ-5D-5L)

The Euro-QOL, Five Dimensions, Five Levels (EQ-5D-5L) questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D-5L comprises 2 components: a questionnaire covering 5 dimensions and a tariff of values based upon direct valuations of health states using a visual analog scale (VAS).

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

This questionnaire takes approximately 5 minutes to complete.

### 7.12.3. Work Productivity and Activity Impairment Questionnaire (WPAI)

The Work Productivity and Activity Impairment Questionnaire (General Health V2.0 [WPAI:GH]; see Appendix C) measures work and activity impairment during the past 7 days. It contains 2 domains: work and activity.

- The work domain includes 5 items that ask the subject about how many hours of work were missed due to health problems, how many hours of work missed due to other reasons, how many hours the subject worked, and how health problems may have affected productivity.

- The activity domain contains a single item that asks the subject how health problems affected his or her ability to do regular activities outside of their work.

The WPAI yields 4 types of scores: absenteeism, presenteeism, work productivity loss, and activity impairment. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

This questionnaire takes approximately 2 to 3 minutes to complete.

## 7.13. Biomarkers

Biomarker analysis will be performed on product, blood, and tumor samples to evaluate predictive, pharmacokinetic (PK), and pharmacodynamic markers for axicabtagene ciloleucel.

A FFPE tumor block or 30 unstained slides are required. Should an archived tumor sample not be available, a fresh tumor sample is required prior to start of chemotherapy to continue on study. Slides that have been previously stained with antibodies or other reagents are not acceptable.

Tumor tissue analysis will include evaluation of CD19 expression by immunohistochemistry (IHC), gene expression profiling for cell of origin analysis, and central analysis of DNA alterations for sub-classification of DLBCL double- and triple-hit status. CCI [redacted]

Additional clinical specimens may be obtained as needed to assess safety in subjects or if novel findings are observed in this study.

For subjects randomized to the axicabtagene ciloleucel arm:

- Blood draws for levels of anti-CD19 CAR T cells in blood
- Blood draws for evaluation of serum cytokines and chemokines. The following cytokines may be included in the panel: homeostatic, pro-inflammatory and immune modulating cytokines IL-2, IL-6, IL-10, IL-12p40/p70, IL-15, IL-17a, tumor necrosis factor (TNF)-α, IFN-γ, GM-CSF, and CRP, HLH related markers ferritin and IL-2Rα and chemokines MIP-1α, MIP-1β, and IL-8.
- CSF, and additional subject samples (eg, pleural fluid), will be obtained from subjects who develop Grade ≥ 2 neurologic events to enable evaluation of inflammatory cytokine and chemokine levels and also presence of anti-CD19 CAR T cells. As applicable, lymphocyte populations residing in the CSF, or other subject samples, may also be monitored for the purpose of understanding the safety profile of axicabtagene ciloleucel.
- Blood draws for RCR analysis (see Section 7.11.2.2).
- A baseline serum sample and additional serum samples outlined in the SOA may be analyzed for development of antibodies if a treatment-related hypersensitivity reaction is observed.
- Baseline leukapheresis and final axicabtagene ciloleucel samples will be collected and analyzed by immunophenotyping, qPCR, and/or gene expression profiling. CCI [redacted]

CCI [redacted] Each subject will have the right to have the sample material destroyed at any time by contacting the investigator who, in turn, can contact the central laboratory. The investigator should provide the sponsor with the study and subject 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.

### 7.14. Post-treatment Follow-up

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

For subjects randomized to the axicabtagene ciloleucel arm of the study, if at any time during the post-treatment assessment period a subject did not respond to treatment, the subject will continue to undergo follow-up procedures and then be followed for survival and disease outcomes in the long-term follow-up portion of the study.

Subjects randomized to the SOC arm and who respond to SOC therapy after 2 or 3 cycles (defined as achieving a PR or CR) should proceed to HDT and ASCT per institutional or national guidelines as outlined in Section 6.3.1.1. Subjects who are alive and do not have documented disease progression will continue to be followed for disease progression.

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

**Table 2. Schedule of Assessments Axicabtagene Ciloleucel Arm**

| Procedures | Screening | Randomization | Leukapheresis | Conditioning Chemotherapy | | | | | IP Administration | | Post Treatment Follow-up All Post Treatment visits are calculated from date of randomization | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Within 14 days of randomization | | Within approx. 5 days after randomization | d-5 | d-4 | d-3 | d-2 | d-1 | Treatment d0 | d1 – 7[m] | Day 50 (-7 to +21 days) | Day 100 (± 14 days) | Day 150 (± 14 days) |
| Medical history | X | | | | | | | | | | | | |
| Physical exam[a] | X | | | | | | | | | | X | X | X |
| Neurological assessment | X | | | | | | | | X[b] | QOD[b] | X | | |
| Weight (plus height at screening) | X | | X | | | | | | | | | | |
| Vital signs (BP, HR, RR, O2 sat, temp) | X | | X | | | | | | | | X | X | X |
| ECOG performance status | X | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | |
| ECHO[c] | X | | | | | | | | | | | | |
| PET-CT disease assessment[d] | PET-CT[d] | | | | | | | | | | PET-CT | PET-CT | PET-CT |
| Archived tumor sample[e] | X[e] | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | X | | | | | | | | | | | | X |
| Blood draw for chemistry panel | X | | X | X | | | | | X | X | X | X | X |
| Blood draw for CBC w/differential | X | | X | X | | | | | X | X | X | X | X |
| Blood draw for anti-axicabtagene ciloleucel antibodies[f] | | | X | | | | | | | | X[f] | | |
| Blood draw for LDH | X | | | | | | | | | | | | |
| IXRS/Randomization call | | X | | | | | | | | | | | |
| Lumbar Puncture[g] | | | | | | | | | | X[g] | | | |
| Blood draw for CRP/Ferritin | | | X | | | | | | X | X | | | |

| Procedures | Screening | Randomization | Leukapheresis | Conditioning Chemotherapy | | | | | IP Administration | | Post Treatment Follow-up All Post Treatment visits are calculated from date of randomization | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Within 14 days of randomization | | Within approx. 5 days after randomization | d-5 | d-4 | d-3 | d-2 | d-1 | Treatment d0 | d1 – 7[m] | Day 50 (-7 to +21 days) | Day 100 (± 14 days) | Day 150 (± 14 days) |
| Blood draw for PBMCs and additional analysis[h] | | | X | | | | | | | d1, 3 & 7[h] | X[h] | X[h] | X[h] |
| Blood draw for cytokines[h] | | | X | | | | | | X | d1, 3 & 7[h] | X[h] | | X[h] |
| Blood draw for serology (EU sites)[l] | X[l] | | X[l] | | | | | | | | | | |
| EORTC QLQ-C30[i] | X | | | X | | | | | X | | X | X | X |
| EQ-5D-5L[i] | X | | | X | | | | | X | | X | X | X |
| WPAI[i] | X | | | X | | | | | X | | X | X | X |
| Leukapheresis | | | X | | | | | | | | | | |
| Fludarabine/Cyclophosphamide | | | | X | X | X | | | | | | | |
| Axicabtagene ciloleucel infusion IV | | | | | | | | | X | | | | |
| Adverse events[j]/ Concomitant medication[k] | X | | X | X | X | X | X | X | X | X | X | X | X |

Abbreviations: D, day; IP, investigational product; BP, blood pressure; HR, heart rate; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; PET-CT, positron emission tomography computer tomography; CBC, complete blood count; LDH, lactate dehydrogenase; IXRS, Interactive Voice/Web (X) Response System; CRP, C-reactive protein; PBMC, peripheral blood mononuclear cell; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EQ-5D-5L,Euro-QOL, Five Dimensions, Five Levels; WPAI, Work productivity and activity impairment questionnaire.

a Physical Exam: Subjects with new-onset symptoms related to CRS should undergo physical examination at least daily until symptoms resolve to baseline. Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam will have a brain MRI and lumbar puncture for examination of cerebral spinal fluid.

b Neurologic assessment: A neurological assessment should be done prior to axicabtagene ciloleucel infusion on treatment day 0, then on treatment day 1 and every other day during the minimum 7-day observation period. For new onset of neurologic symptoms, neurologic assessment should be performed at least daily until symptoms resolve to baseline.

c Echo: Performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility

d PET-CT disease assessment: PET-CT should be performed as close to randomization as possible and within 28 days prior to randomization. If bone marrow involvement was not evaluated at the time of relapse and within 28 days of study entry, a PET-CT or a bone marrow biopsy will be performed to establish a baseline. PET-CT shall be performed at any time disease progression is suspected. If there is evidence of baseline bone marrow involvement, if PET-CT is not available or if there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm complete response.

e Archived tumor sample: Archived tumor samples will be submitted to central laboratory for evaluation of CD19 expression and prognostic variables. Either FFPE tumor block or 30 unstained slides are required. Should an archived tumor sample not be available, a fresh tumor sample is required prior to start of chemotherapy to continue on study. Slides that have been previously stained with antibodies or other reagents are not acceptable. Screen failed subjects' archived samples should not be submitted.

f Blood draw for anti-axicabtagene ciloleucel antibodies: Baseline antibody samples to be collected prior to start of leukapheresis. If positive at baseline or Day 50 additional samples will be collected every 3 months until titers return to baseline or up to 12 months post axicabtagene ciloleucel infusion.

g Lumbar Puncture: Subjects with new onset Grade ≥ 2 neurologic symptoms post axicabtagene ciloleucel infusion will have lumbar puncture performed to assess cerebral spinal fluid.

h Blood draws for PBMCs, cytokines, and additional analysis per Section 7.11.2: PBMC blood will be used for the analysis of tests that include anti-CD19 CAR T cells, lymphocytes, and RCR, and will be collected at baseline (prior to initiation of conditioning chemotherapy), day 1, 3, 7 and study Days 50, 100, and 150. Blood draws for cytokines will be collected at baseline (prior to initiation of conditioning chemotherapy), treatment day 0, 1, 3, 7, and study Days 50 and 150. Blood draws for RCR will be collected at baseline, study Day 150, and then per LTFU SOA. If, following the minimum 7-day observation period, the subject is 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 admission, then weekly, and on day of discharge. If the subject experiences a Grade ≥3 axicabtagene ciloleucel-related toxicity such as Grade 3 CRS or neurologic event, one additional blood draw for cytokines will be taken at the time of the Grade ≥3 axicabtagene ciloleucel-related toxicity and upon resolution of the event. Blood and serum samples may also be used for further anti-CD19 CAR T cell, RCR and immunogenicity evaluation as clinically indicated.

i EORTC QLQ-C30/EQ-5D-5L/WPAI: To be completed by the subject before any procedures are performed-excluding blood draws.

j Adverse Events: The investigator is responsible for reporting all adverse events observed by the investigator or reported by the subject that occur after randomization through the Day 150 post-randomization visit or until the initiation of new lymphoma therapy, whichever occurs first.

k Concomitant medications should be recorded from the date of the informed consent through the Day 150 post-randomization visit, and targeted concomitant therapies from this visit until Month 12, or until a change in lymphoma therapy, or disease progression whichever occurs first.

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

m Subjects will be monitored daily through day 7 after treatment with axicabtagene ciloleucel unless otherwise required by country regulatory agencies (refer to Appendix D). All assessments described in this table for day 1-7, are applicable between days 7 and 10 if required by country regulatory agencies.

**Table 3. Schedule of Assessments SOC Chemotherapy Arm**

| Procedures | Screening | Randomization | Treatment Period Cycle 1 and Cycle 2 | | Disease Assessment calculated from date of randomization | Treatment Period HDT-ASCT or Cycle 3–HDT-ASCT (optional) | Post Treatment visits are calculated from date of randomization | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Post HDT-ASCT | Post Tx FU |
| Day | Within 14 days of randomization | | Cycle 1 Within approx. 5 days after randomization | Cycle 2 | Day 50 (-7 to +21 days) | HDT-ASCT or Cycle 3-HDT-ASCT | D100 (± 14 days) | Day 150 (± 14 days) |
| Medical history | X | | | | | | | |
| Physical exam[a] | X | | | | X | | X | X |
| Neurological assessment | X | | | | X | | | |
| Weight (plus height at screening) | X | | | | | | | |
| Vital signs (BP, HR, RR, O2 sat, temp) | X | | | | X | | X | X |
| ECOG performance status | X | | | | | | | |
| ECG | X | | | | | | | |
| ECHO[b] | X | | | | | | | |
| PET-CT disease assessment[c] | PET-CT[c] | | | | PET-CT | | PET-CT | PET-CT |
| Archived tumor sample[d] | X | | | | | | | |
| Pregnancy test (serum or urine) | X | | | | | | | X |
| Blood draw for chemistry panel | X | | X | X | X | X | X | X |
| Blood draw for CBC w/differential | X | | X | X | X | X | X | X |
| Blood draw for LDH | X | | | | | | | |
| Blood draw for additional analysis[j] | | | X | | X | | X | X |
| IXRS / Randomization call | | X | | | | | | |
| EORTC QLQ-C30[e] | X | | X | | X | day of transplant | X | X |
| EQ-5D-5L[e] | X | | X | | X | day of transplant | X | X |
| WPAI[e] | X | | X | | X | day of transplant | X | X |
| SOC chemotherapy[f] | | | X | X | | X (Cycle 3 is optional) | | |

| Procedures | Screening | Randomization | Treatment Period Cycle 1 and Cycle 2 | | Disease Assessment calculated from date of randomization | Treatment Period HDT-ASCT or Cycle 3–HDT-ASCT (optional) | Post Treatment visits are calculated from date of randomization | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Post HDT-ASCT | Post Tx FU |
| **Day** | **Within 14 days of randomization** | | **Cycle 1 Within approx. 5 days after randomization** | **Cycle 2** | **Day 50 (-7 to +21 days)** | **HDT-ASCT or Cycle 3-HDT-ASCT** | **D100 (± 14 days)** | **Day 150 (± 14 days)** |
| Leukapheresis[g] | | | | | | X[g] | | |
| HDT[g] | | | | | | X[g] | | |
| $CD34^+$ stem cell infusion[g] | | | | | | X[g] | | |
| Adverse events[h]/ Concomitant medication[i] | X | | X | X | X | X | X | X |

Abbreviations: HDT, high-dose therapy; ASCT, autologous stem cell transplant; Tx, treatment; FU, follow-up; BP, blood pressure; HR, heart rate; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; PET-CT, positron emission tomography computer tomography; CBC, complete blood count; LDH, lactate dehydrogenase; IXRS, Interactive Voice/Web (X) Response System; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EQ-5D-5L,Euro-QOL, Five Dimensions, Five Levels; WPAI, Work productivity and activity impairment questionnaire; SOC, standard of care.

a Physical Exam: Subjects with symptoms of central nervous system malignancy such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam will have lumbar puncture for examination of cerebral spinal fluid.

b Echo: Performed following the subjects last chemotherapy treatment and within 28 days prior to signing the consent may be used for confirmation of eligibility.

c PET- CT disease assessment: PET-CT should be performed as close to randomization as possible and within 28 days prior to randomization. If bone marrow involvement was not evaluated at the time of relapse and within 28 days of study entry, a PET-CT or a bone marrow biopsy will be performed to establish a baseline. PET-CT should be performed at any time disease progression is suspected. If there is evidence of baseline bone marrow involvement, if PET-CT is not available or if there are unexplained cytopenias or suspicion of bone marrow involvement, a bone marrow aspirate and biopsy will be performed in subjects who are being assessed for CR in order to confirm complete response.

d Archived tumor sample: Archived tumor samples will be submitted to central laboratory for prognostic variables. Either FFPE tumor block or 30 unstained slides are required. Should an archived tumor sample not be available, a fresh tumor sample is required prior to the start of second-line combination chemotherapy regimen to continue on study. Slides that have been previously stained with antibodies or other reagents will not be acceptable for study entrance. Screen failed subjects' archived samples should not be submitted.

e EORTC QLQ-C30/EQ-5D-5L/WPAI: To be completed by the subject before any procedures are performed-excluding blood draws.

f SOC Dosing and Administration Refer to Section 6.3.1 for investigator choice of SOC regimens and dosing details. If adequate disease response (CR or PR) is demonstrated after the second or third cycle of chemotherapy, HDT-ASCT may be initiated.

g Leukapheresis, HDT, and CD34+ stem cell infusion procedures performed for subjects undergoing HDT-ASCT only. This occurs if adequate disease response (CR or PR) is demonstrated after two or three cycles of chemotherapy.

h Adverse Events: The investigator is responsible for reporting all adverse events observed by the investigator or reported by the subject that occur after randomization through the Day 150 post-randomization visit or until the initiation of new lymphoma therapy, whichever occurs first.

i Concomitant medications will only be recorded from the date of the informed consent through 30 days after the last study specific procedure.

j Blood draws for additional analyses per Section 7.11.2.

### 7.15. Long-term Follow-up (Axicabtagene Ciloleucel and Standard of Care Arms)

All subjects will be followed in the long-term follow-up period for disease assessments and survival status per the SOA (Table 4) until the transition to the separate LTFU study. Subjects will begin the long-term follow-up period beginning at the Month 9 visit and will be assessed as follows:

- Every 3 months (± 28 days) through Month 24
- Every 6 months (± 28 days) between Month 24 and Month 60

**SOC Arm Only:**

- All subjects in the SOC arm will discontinue participation in the study after completion of the Month 60 visit and assessments.

**Axicabtagene Ciloleucel Arm Only:**

- After Month 60, all subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will return to the clinic once annually for up to 15 years.
- All subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will be transitioned to the separate LTFU study after providing signed informed consent for the LTFU study and after completing at least 60 months of assessments in the parent study, KTE-C19-107. Until this time point, subjects will complete the post-treatment follow up period as per the SOA (Table 4).
- In the LTFU study, subjects will continue assessments at timepoints contiguous with the long-term follow up period time points in this study.

**SOC and Axicabtagene Ciloleucel Arms:**

Subjects who did not respond to treatment may receive off protocol therapy but will continue to be followed for disease assessments (if progression was not documented), subsequent anticancer therapy, and survival.

Subjects may also be contacted by telephone to confirm survival status and subsequent new lymphoma therapy use. Should a subject require lab collection, labs may be collected at the clinic or at an outside facility to reduce the subject burden.

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

Subjects who are unable or unwilling to return to the study site may have follow up data for this period obtained from clinical, laboratory, and/or diagnostic assessments conducted by the referring healthcare provider (HCP) and/or general practitioner (GP). In addition, other health status information may be obtained from the subject and/or the subject's referring HCP and/or GP via telephone or email communication. This information will be used to detect late-onset targeted SAEs that may be related to study therapy.

Subjects and/or the subject's referring HCPs and/or GPs may be contacted directly by telephone or email to confirm survival status and obtain information about targeted concomitant medication use, subsequent anticancer therapy use, and late-onset targeted SAEs (if the SAE does not require a test to be performed in the clinic).

Refer to the SOA (Table 4) for a listing of study procedures and disease assessments to be completed during the long-term follow-up period.

Subjects who are enrolled/randomized but did not receive investigational product, or received therapy but didn't respond to treatment, will be followed in the long-term follow-up period until Month 60 (refer to Section 3.5.3) and will undergo the following assessments at the time points outlined in the SOA (Table 4):

- Subsequent therapy for the treatment of NHL
- Survival status: Subjects and/or the subject's referring HCPs and/or GPs may be contacted directly by telephone or email to assess survival status
- Disease assessments per protocol
- AEs/SAEs per Section 9

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

| Procedure | Long-term Follow-up Period 1 Each visit calculated from randomization (all visits have ± 28 day window) | | | | | | | | | | | | Long-term Follow-up Period 2 Each visit calculated from randomization (all visits have ± 3 month window) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Axicabtagene Ciloleucel Arm and Standard of Care Arm | | | | | | | | | | | | Axicabtagene Ciloleucel Arm Only |
| **Visit frequency** | **Month 9** | **Month 12** | **Month 15** | **Month 18** | **Month 21** | **Month 24** | **Month 30** | **Month 36** | **Month 42** | **Month 48** | **Month 54** | **Month 60** | **Month 72 and Annually Thereafter to 15 Years*** |
| Physical exam[a] | X | X | X | X | X | X | | | | | | | |
| PET-CT scan/CT Scan disease assessment[b] | PET-CT | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | PET-CT/CT[b] | X[b] |
| Survival status[c] | X | X | X | X | X | X | X | X | X | X | X | X | X[c] |
| CBC w/differential[d] | X | X | X | X | X | X | | | | | | | |
| Blood draw for PBMCs and additional analysis[e] | X | X | | X | | X | | X | | X | | X | X[e] |
| Targeted SAEs[f] | X | X | X | X | X | X | X | X | X | X | X | X | X[f] |
| Subsequent therapy for NHL[g] | X | X | X | X | X | X | X | X | X | X | X | X | X[g] |
| PROs[h] | X | X | X | X | X | X | | | | | | | |

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

*After completing at least 60 months of assessments in this study, all subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will be transitioned to a separate LTFU study, after providing informed consent, to complete the remainder of the 15-year follow-up period.

a Physical exams will continue through the first 24 months

b PET-CT will continue through Month 9 or until disease progression, whichever comes first. If subject's disease has not progressed by Month 9, disease assessments will be evaluated per CT scans where a CR is suspected and per PET-CTs where a PR is suspected. PET-CT should be performed at any time disease progression is suspected. If subject's disease has not progressed by Month 60, the status of the subject's primary malignant disease will be monitored per local standard of care. The subject's disease status does not need to be assessed at the investigative site. Records from the referring HCP and/or GP may be obtained for subjects who are unable or unwilling to return to the investigative sites.

c Survival status: Subjects and/or the subject's referring HCPs and/or GPs may be contacted directly by telephone or email to assess survival status.

d CBC w/differential: Subjects will continue to provide samples for CBC w/diffs and lymphocyte subsets through Month 24.
e Blood draws for analysis, such as RCR (for subjects randomized into the axicabtagene ciloleucel arm), PBMCs, and additional analysis per Section 7.11.2 and the timepoints specified in the laboratory manual. Samples for RCR will continue to be collected yearly until transition to the LTFU study and tested as clinically indicated.
f Targeted SAEs are defined as and include neurological, hematological, infections, autoimmune disorders, and secondary malignancies and should be reported for up to 5 or 15 years for SOC or axicabtagene ciloleucel arms, respectively, or until disease progression, whichever occurs first. After Month 60 targeted SAEs will be reported through 15 years or until disease progression and/or start of subsequent anticancer therapy, whichever occurs first. These events will be identified from routine safety assessments (ie, physical examination and laboratory assessments) performed as standard of care (not required to be performed at the study site).
g Subsequent therapy will be collected for all enrolled subjects until the end of the subject's participation in this study or, while still a participant in this study, the subject is considered lost to follow-up, withdraws consent, or dies. Subjects and/or the subject's referring HCPs and/or GPs may be contacted directly by telephone or email to collect information about subsequent therapy.Refer to Sections 6.2.6 and 6.3.4 for more details.
h PROs include the following assessments: EORTC QLQ-C30, EQ-5D-5L, & WPAI

# 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 certain follow-up elements of 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 including the following:

- Survival status, including the cause of death
- Safety reporting, including new malignancies; SAEs related to axicabtagene ciloleucel and targeted SAEs including, but not limited to, neurologic events, infections, blood disorders, or immune disorders; and pregnancies
- Targeted concomitant medications as per the SOA and Section 6.2.4.9
- Subsequent therapies
- Central laboratory samples (per 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, publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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:

- AE
- Disease progression
- Subject request/noncompliance
- 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
- Termination of the study by the sponsor
- Other (eg, noncompliance)

# 9. SAFETY REPORTING

## 9.1. Adverse Events

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

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (eg, more frequent headaches for a subject with pre-existing headaches). A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

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

The term "disease progression" as assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported with the preferred term "B-cell lymphoma".

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

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. In the event of a subject requests to withdraw from protocol-required therapies or the study due to an AE, the subject should undergo the procedures outlined in the Day 150 post-randomization visit of the SOA.

## 9.2. Reporting of Adverse Events

The investigator is responsible for reporting all AEs observed by the investigator or reported by the subject that occur after randomization through the Day 150 post-randomization visit or change in lymphoma therapy, whichever occurs first. For subjects who are enrolled but do not receive axicabtagene ciloleucel, the AE reporting period ends 30 days after the last procedure (eg, leukapheresis, conditioning chemotherapy).

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

- AE diagnosis or syndrome (if not known, signs or symptoms)

- Dates of onset and resolution
- Severity
- Assessment of relatedness to 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). CRS events will be reported using the grading scale outlined in the Investigator Brochure.

In reviewing adverse events, investigators must assess whether the adverse event is possibly related to 1) axicabtagene ciloleucel or SOC chemotherapy, 2) conditioning chemotherapy (for subjects enrolled into the axicabtagene ciloleucel arm of the study), 3) any protocol-required study procedure or treatment (ie, HDT ASCT), 4) disease progression, 5) concurrent disease, 6) concomitant medication, or 7) other. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs.

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

### 9.2.1. Reporting Abnormal Laboratory Findings

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

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

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

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

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

## 9.4. Reporting of Serious Adverse Events

The investigator is responsible for reporting all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through the Day 150 post-randomization visit or until the initiation of new lymphoma therapy, whichever occurs first. After the Day 150 post-randomization visit only targeted SAEs will be reported. Targeted SAEs are defined as and include neurological, hematological, infections, autoimmune disorders, and secondary malignancies and should be reported for up to 5 or 15 years for SOC or axicabtagene ciloleucel arms, respectively, or until disease progression, whichever occurs first.

Serious adverse events, which the investigator assesses as related to axicabtagene ciloleucel, should be reported regardless of the time period.

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

All SAEs must be submitted via email to Safety_FC@gilead.com within 24 hours following the investigator's knowledge of the event. After the electronic SAE system is available, all SAEs must be submitted to Kite via the eSAE system within 24 hours of the investigator's knowledge of the event. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and emailed to the SAE Reporting mailbox: Safety_FC@gilead.com.

After completion of this study and database closure, any relevant information on ongoing SAEs must be submitted to Kite within 24 hours after the investigator's knowledge of the event using the portable document format (PDF) version of the paper SAE Report Form and sent via e-mail to the SAE Reporting mailbox: Safety_FC@gilead.com.

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

Disease progression of the malignancy is not considered an AE. However, signs and symptoms of disease progression may be recorded as AEs or SAEs and indicated as due to disease progression on the eCRF. If the malignancy has a fatal outcome before Day 150 post-randomization visit, then the event "B-cell lymphoma" must be recorded as an SAE with the outcome fatal.

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

Any death occurring after randomization and prior to Day 150 post-randomization visit, regardless of attribution to treatment, requires expedited reporting within 24 hours. Any death occurring after the Day 150 post-randomization visit requires expedited reporting within 24 hours only if it is considered related to treatment.

### 9.4.1. Reporting Deaths

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

## 9.5. Diagnosis Versus Signs and Symptoms

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

## 9.6. Pregnancy and Lactation

There is no relevant clinical experience with axicabtagene ciloleucel in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. 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. Refer to Appendix E for the definition of childbearing potential.

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

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

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. Any SAE occurring as an adverse pregnancy outcome after the study has been completed must be reported to Kite Patient Safety and Pharmacovigilance.

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

Pregnancies of female partners of male study subjects exposed to axicabtagene ciloleucel or other study drugs must also be reported and relevant information should be submitted to Kite Patient Safety and Pharmacovigilance using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Kite Patient Safety and Pharmacovigilance.

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

### 9.7. Hospitalization and Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be SAEs:

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

### 9.8. Abnormal Vital Sign Values

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

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

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

### 9.9. Data Safety Monitoring Board

An independent DSMB will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed.

The DSMB will also review SAE information and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout subject treatment in the study. The DSMB may request additional safety or efficacy data or recommend modifying the study conduct. The sponsor may request additional reviews by the DSMB. Data submitted to the DSMB may be monitored or unmonitored to facilitate timely DSMB review.

At the time of expedited reporting of SUSARs to FDA, Kite Pharma (or designee) will concurrently submit these reports to the DSMB Chair. The DSMB Chair will also review SAE narrative reports monthly.

# 10. STATISTICAL CONSIDERATIONS

## 10.1. Hypothesis

The hypothesis is that axicabtagene ciloleucel will prolong EFS compared to SOC therapy in adult subjects with relapsed/refractory DLBCL. The hypothesized treatment effect corresponds to a 50% improvement in the EFS time.

## 10.2. Study Endpoints

### 10.2.1. Primary

EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy, or death from any cause. The following criteria will be used to further define events and event times:

- Subjects with established PR or CR and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the last evaluable disease assessment prior to the new lymphoma therapy

- Subjects with best response of SD and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the first time SD was established prior to the new lymphoma therapy

- Subjects who commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date

- Subjects with best response of SD up to and including Day 150 assessment post-randomization will be considered to have an EFS event. For such subjects, the EFS time will be defined as the time from randomization to the first time SD was established up to and including the Day 150 disease assessment

The following criteria will be used to further define censoring times:

- Subjects alive, in response, and with no new therapy will be censored at the last evaluable disease assessment

- Subjects with no evaluable disease assessment by Day 150 assessment post-randomization will not be considered to have an EFS event, and the EFS time will be censored at the randomization date

- The EFS time for subjects in the axicabtagene ciloleucel arm who undergo SCT in the absence of any documented progression or new therapy will be censored on the day of SCT

- For subjects in the SOC arm, TBI, HDT, and SCT that occur while the subject is in response from protocol-specified induction therapy will not be considered an EFS event. The EFS time for SOC arm subjects alive, progression-free, and with no new lymphoma therapy will be censored at the last evaluable disease assessment date

- At the time of the interim analysis of EFS, subjects who have not had the opportunity to be followed to the Day 150 disease assessment and who do not have an EFS event will be censored at the last evaluable disease assessment prior to Day 150

For the primary analysis of EFS, disease progression events and censoring times will be determined by blinded central review. Events of subsequent new lymphoma therapy and death will be based on the clinical trial database. A sensitivity analysis for EFS in which subjects in the axicabtagene ciloleucel arm who undergo SCT while in an axicabtagene ciloleucel-induced response are imputed to have an EFS event at the time of SCT will be performed.

The primary analysis of EFS will be conducted when all subjects have had the opportunity to be followed to the Month 9 disease assessment, and 250 EFS events have been observed. If more than 250 EFS events are observed at the time of the data cutoff for the primary analysis, all observed events will be used in the analysis.

At the time of the interim analysis of EFS, subjects who have not had the opportunity to be followed to the Day 150 disease assessment and who do not have an EFS event will be censored at the last evaluable disease assessment prior to Day 150.

### 10.2.2. Key Secondary

ORR is defined as the incidence of either a complete response or a partial response by the Lugano Classification {Cheson 2014} as determined by blinded central review. All subjects that do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders. For the derivation of ORR in both arms, disease assessments obtained after randomization and up through an observation of progression per Lugano Classification will be used. In both arms, derivation of best response will include all assessments until an EFS event, including any assessments obtained after SCT for the SOC arm.

OS is defined as the time from randomization to death from any cause. Subjects who have not died by the analysis data cutoff date will have survival time censored at their last date known to be alive. For subjects alive or dead after the data cutoff date, survival time will be censored at the data cutoff date.

### 10.2.3. Secondary

EFS based on investigator disease assessments: EFS based on investigator disease assessments will use the same definition as EFS, except that progression events and censoring times will be based on the investigator disease assessments.

Modified EFS (mEFS): mEFS is defined the same way as EFS, except that failure to attain CR or PR by Day 150 assessment is not considered as an event. mEFS will be analyzed per blinded central review and per investigator disease assessments.

PFS is defined as the time from randomization to disease progression per Lugano Classification {Cheson 2014} as determined by investigator review or death from any cause. Subjects alive and not meeting the criteria for progression at the analysis data cutoff date will have PFS time censored at the last evaluable disease assessment. Subjects who receive subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and SCT while in a protocol therapy induced response) in the absence of documented disease progression will be censored at their last evaluable disease assessment date prior to the commencement of the subsequent new lymphoma therapy. SCT that occurs while a subject is in response from a protocol therapy will not be considered a PFS event, and such subjects will be censored for PFS at the of the last evaluable disease assessment date prior to the SCT for subjects in the axicabtagene ciloleucel arm and will be censored at the last evaluable disease assessment date including assessments after SCT for subjects in the SOC arm for the primary analysis of PFS. Disease outcomes will be based on investigator assessment.

DOR is derived only among subjects who experience an objective response per Lugano Classification {Cheson 2014} as determined by blinded central review and is defined as the time from first objective response to disease progression per the Lugano Classification or death from any cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will have DOR censored at their last evaluable disease assessment date. Subjects who receive subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and SCT while in a protocol therapy induced response) in the absence of documented progression will have DOR censored at the last evaluable disease assessment prior to the commencement of the new lymphoma therapy. For the primary analysis of DOR, DOR will be censored at the last evaluable disease assessment date prior to the SCT for subjects undergo SCT while in protocol therapy induced response in the axicabtagene ciloleucel arm, and will be censored at the last evaluable disease assessment date including assessments after SCT for subjects in the SOC arm.

Incidence of adverse events and clinical significant changes in safety lab values, including antibodies to axicabtagene ciloleucel.

Changes in EORTC QLQ-C30 domains from screening to post baseline.

Changes in the EQ-5D-5L index and VAS scores from screening to post baseline.

CCI [redacted]

CCI [redacted]

### 10.2.5. Analysis Subsets

The primary analysis of all efficacy endpoints, unless noted otherwise, will be conducted on the full analysis set (FAS), defined as all randomized subjects. Subjects will be analyzed according to the treatment first randomized regardless of treatment received.

The safety analysis set is defined as the subset of all randomized subjects who receive at least one dose of axicabtagene ciloleucel as protocol therapy or SOC chemotherapy as protocol therapy. Subjects will be analyzed by the protocol therapy received.

The safety analysis set – ASCT is defined as the subset subjects randomized to the SOC arm who undergo transplant as part of protocol therapy.

The primary analysis of HRQoL will be performed on the subset of subjects in the FAS who have a baseline and at Day 150 post-randomization assessment.

### 10.2.6. Covariates

The following baseline covariates may be used to examine efficacy and/or safety in subgroups or covariate analyses:

- Geographic region (North America, Europe)
- ECOG performance status at screening (0, 1)
- Age at randomization ($\geq 65$, $< 65$)
- Sex
- Race/ethnicity
- Response to first-line therapy (primary refractory, relapse $\leq 6$ months of first line therapy vs relapse $> 6$ and $\leq 12$ months of first-line therapy)
- Age-adjusted IPI (0 to 1 vs 2 to 3) at time of screening

- Disease type (DLBCL, TFL)
- Molecular subgroup (germinal center B-cell like [GBC], activated B-cell like [ABC])
- Double hit (C-MYC alterations and either BCL-2 or BCL-6 alterations) status by FISH
- Triple hit (BCL-2, BCL-6, and C-MYC alterations) status by FISH

For the primary analysis of efficacy, the IXRS values of response to first-line therapy and age-adjusted IPI will be used. Sensitivity analyses may be conducted with values collected in EDC. Covariate levels that are sparse (ie, less than 30 events for time to event analyses or subjects for ORR analyses) may be collapsed for purposes of statistical modeling. If this occurs, the strata for relapse ≤ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy will be collapsed first.

### 10.3. Sample Size Considerations

An EFS hazard ratio (test/control arm) of 0.67 is hypothesized in the FAS set. Assuming an exponential distribution for EFS and a median EFS of 4 months in the SOC arm, this implies a 50% relative improvement in EFS and corresponds to median EFS of 4 versus 6 months (control vs test arm). The primary analysis is planned when 250 EFS events have been observed; the study has been sized to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS. The minimum effect size that can be determined to be statistically significant is an EFS hazard ratio of 0.79, or a 27% relative improvement in EFS. Further, assuming a concave accrual distribution with 50% of accrual in the last 33% of the accrual period of 24 months and a 10% rate (5% by month 1 and cumulative 10% by month 8) of loss to follow-up in the axicabtagene ciloleucel arm and 15% rate (10% by month 1 and cumulative 15% by month 8) of loss to follow-up in the SOC arm, it is anticipated that the event goal will be achieved if 350 subjects are randomized (175/arm) and will occur approximately 31 months after the first subject is randomized. One interim futility analysis of EFS will be conducted after 135 EFS events have been observed. The interim analysis will not allow early stopping for efficacy.

The study will have an overall alpha of 2.5% with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints will follow a hierarchical scheme. EFS will be tested first at the primary EFS analysis. Conditional on a statistically significant improvement in EFS, ORR will be tested at the 2.5% level at the time of the primary EFS analysis. Conditional on a statistically significant improvement in EFS and ORR, OS will be tested up to 3 times at an overall 1-sided alpha level of 2.5%.

For the analysis of ORR, response rates of 36% and 78% in the control and test arms are assumed. ORR will be tested with a stratified (randomization factors) Cochran-Mantel-Haenszel test at the 2.5% level among subjects with measurable disease at baseline.

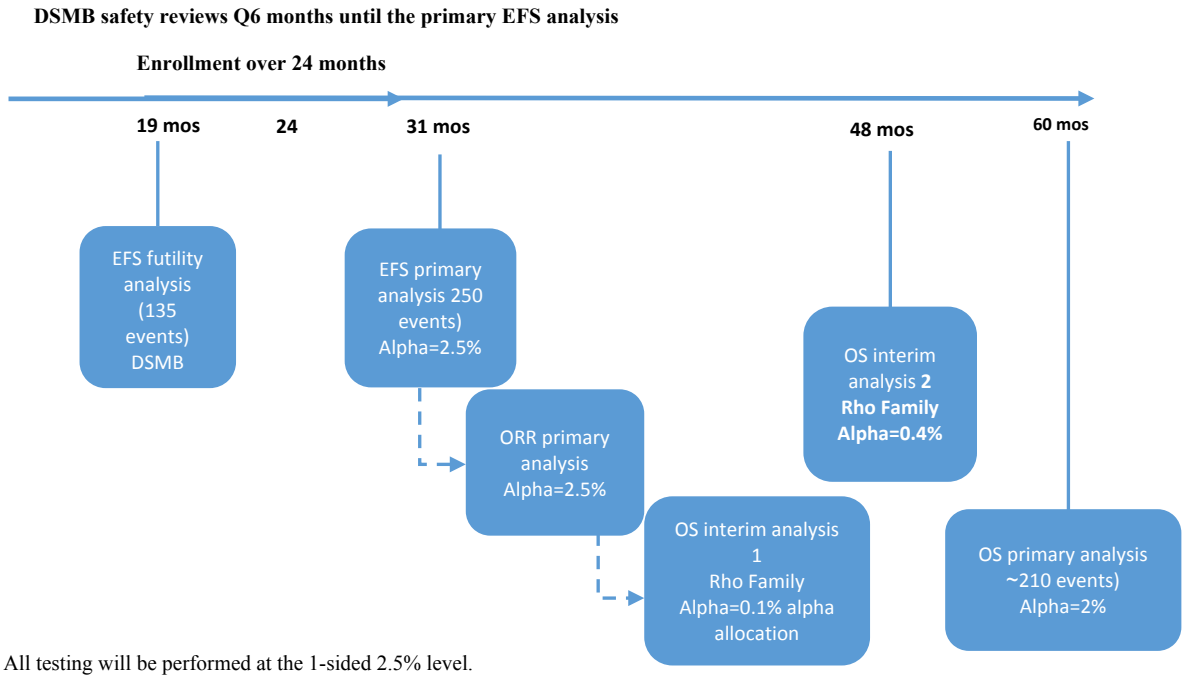
An OS hazard ratio of 0.73 is hypothesized in the FAS set. Assuming an exponential distribution for OS and a median OS of 15.8 months in the control arm, this implies a 37% relative improvement in OS and corresponds to median OS of 15.8 versus 21.6 months. The primary OS analysis is planned when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized with a first interim analysis of OS occurring at the time of primary EFS analysis and a second interim analysis when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized**.**

Stratified (randomization factors) log-rank tests will be used to test the null hypothesis of no difference in EFS and OS using an overall 1-sided alpha level of 2.5%. A stratified (randomization factors) Cochran-Mantel-Haenszel test will be used to test ORR at an overall 1-sided alpha level of 2.5%.

The EFS analyses are event-driven and will occur when the required number of events have been observed.

The study testing scheme is provided in Figure 2.

**Figure 2. Study Testing Scheme**




All testing will be performed at the 1-sided 2.5% level.
Hierarchical testing of EFS, followed by ORR, followed by OS.
Three analyses of OS are planned; a first interim analysis at the time of the primary EFS analysis, a second interim analysis when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized, and a primary OS analysis when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized.
EFS analyses are event-driven and will occur when the required number of events have been observed regardless of anticipating timing.

## 10.4. Access to Individual Subject Treatment Assignments

This is an open-label study where subjects and investigators will be aware of treatment received. Data handling procedures 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 and Trial Integrity Document.

## 10.5. Interim Analysis and Early Stopping Guidelines

### 10.5.1. Safety Interim Analysis

The DSMB will review safety data every 6 months from the time the first subject is randomized until the primary EFS analysis. Additionally, the DSMB will review safety and efficacy data at the time of the planned interim EFS analysis. The DSMB will also review SAE information and SUSARs on a regular basis throughout the study. The sponsor may request additional reviews by the DSMB if safety concerns are identified. The DSMB may meet more often as needed.

### 10.5.2. Efficacy Interim Analysis

One interim analysis of EFS and 2 interim analyses of OS are planned.

The interim EFS analysis is for futility and will occur when 135 EFS events have been observed. An O'Brien-Fleming spending function of the Lan-DeMets family will be used to allocate the type II error between the interim and primary analyses. The futility stopping rule is non-binding. Under the null hypothesis, the probability of stopping for futility at this interim analysis is approximately 60%. One hundred thirty-five (135) EFS events are anticipated to occur approximately 19 months after the first subject is randomized.

Conditional upon statistically significant tests of EFS and ORR, testing of OS will be performed. Two interim analyses of OS will occur, a first at the time of the primary EFS analysis and a second when approximately 160 deaths have been observed or no later than 4 years after the first subject is randomized. A spending function of the Rho family with parameter (rho = 6) will be used to allocate the alpha between the 2 interim analysis of OS and the primary analysis of OS with 0.1% and 0.4% at the interim OS analyses 1 and 2 respectively, and 2% at the primary analysis of OS. Approximately 110 and 160 OS events are anticipated at the time of the interim OS analyses 1 and 2 respectively.

## 10.6. Planned Method of Analysis

The analysis objectives and timing of analyses are described in Section 10.1, Section 10.2, and Section 10.3. Prior to the primary efficacy analysis, modeling and monitoring of cumulative EFS events will be performed to determine a data cutoff date to achieve the planned analysis target event goal.

The primary analysis of EFS will be conducted when all randomized subjects have had the opportunity to be followed to the Month 9 disease assessment and 250 EFS events as determined by blinded central review have been observed. If more than 250 EFS events are observed at the time of the data cutoff for the primary analysis, all observed events will be used in the analysis.

The primary analysis of OS will occur when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized.

Subsequent to data collection for the data cutoff date for the primary analysis of EFS and OS, the total observed number of events will be determined. If this is below the specified lower limit, then a sufficiently later data cutoff date will be used for which the observed total events are at or above the limit.

The interim and primary analyses of EFS will be based on disease progression events and censoring times as determined by blinded central review. A sensitivity analysis of EFS will be based on disease assessments and censoring times based on investigator disease assessment. ORR assessments will be based on blinded central review. Analysis of DOR will use disease assessments based on blinded central review, and analysis of PFS will use disease assessments provided by the investigator.

The Clinical Study Report (CSR) will be written at the time of the primary EFS analysis and will include results of the first interim analysis of OS. Results of the second interim analysis and the primary analysis of OS will be written shortly after each analysis is completed, or no later than 5 years after the first subject is randomized.

### 10.6.1. Event-free Survival

The analysis of EFS will be conducted on the FAS. A stratified (randomization stratification factors) log-rank test will be used for the primary comparison of EFS. Additionally, stratified (randomization factor) Cox regression models will be used to provide the estimated EFS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOC. The median EFS time and event-free rates at 3-month intervals will be provided. The stratification factors as collected in the randomization system at the time of the subjects' randomization will be used for stratified analyses (log-rank test and Cox regression models). Sensitivity analyses will be performed using the actual stratification factor values, in which the strata for relapse $\leq$ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy will be determined based on the time of completion of the first-line therapy.

EFS hazard ratios will be assessed in subgroups defined by covariates in Section 10.2.6.

Sensitivity analyses of EFS will be performed to assess ascertainment time bias in disease progression as follows:

- Progression events that occur in between scheduled assessments will be moved forward to the next scheduled assessment after the observed progression
- Progression events that occur in between scheduled assessments will be moved backward to the last scheduled assessment prior to the progression
- EFS events that occur after more than one missed visit will be censored at the last evaluable disease assessment or visit prior to the observed progression

- Additionally, a sensitivity analysis for EFS will be performed as follows:

- A sensitivity analysis in which subjects in the axicabtagene ciloleucel arm who undergo SCT while in an axicabtagene ciloleucel induced response are considered to have an EFS event on the date of SCT, with EFS time defined as time from randomization to the date of SCT.

EFS based on investigator disease assessments will be analyzed with the same methods as EFS. The concordance of progression events and EFS time per the investigator and per blinded central review will be summarized.

### 10.6.2. ORR

The analysis of ORR will be conducted on the FAS. The subject incidence of objective response and best response will be summarized. An exact binomial 2-sided 95% confidence interval will be generated for the objective response rate and best response rates for each treatment arm. Wilson's score method with continuity correction will be used to calculate 95% confidence intervals for the difference in objective response rates between treatment arms {Newcombe 1998}.

Conditional upon demonstrating a statistically significant improvement in EFS, testing of ORR will be performed with a stratified (randomization factor) Cochran-Mantel-Haenszel test for the common odds ratio of response.

Odds ratios for ORR will be assessed in subgroups defined by covariates in Section 10.2.6.

### 10.6.3. OS

The analysis of OS will be conducted on the FAS. A stratified (randomization stratification factors) log-rank test will be used for the primary comparison of OS. Additionally, stratified (randomization factor) Cox regression models will be used to provide the estimated OS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOC. The median OS time and event-free rates at 6-monthly intervals will be provided. The stratification factors as collected in the randomization system at the time of the subjects' randomization will be used for stratified analyses (log-rank test and Cox regression models). Sensitivity analyses will be performed using the actual stratification factor values, in which the strata for relapse $\leq$ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy will be determined based on the time of completion of the first-line therapy. OS hazard ratios will be assessed in subgroups defined by covariates in Section 10.2.6.

Sensitivity analyses of OS to address the confounding effect from treatment switching, will be conducted using the Rank Preserving Structural Failure Time Model and Inverse Probability of Censoring Weights, 2-stage Cox regression model and CCI [redacted]

### 10.6.4. Progression-free Survival, Duration of Response, and Time to Next Therapy

The analysis of PFS, DOR, and time to next therapy will be performed using the same methods as the analysis of EFS, with p-values from the log-rank test being descriptive.

### 10.6.5. Safety

A TEAE is defined as any AE that begins on or after the first dose of study treatment (axicabtagene ciloleucel infusion or SOC), excluding bridging therapy. Subject incidence rates of TEAEs, including all, serious, fatal, CTCAE Grade 3 or higher, and treatment related AEs reported will be tabulated by preferred term and system organ class coded with the Medical Dictionary for Regulatory Activities (MedDRA). Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

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

The incidence, prevalence, duration, and reversibility of cytopenias will be summarized.

### 10.6.6. Pharmacokinetic Analyses

For subjects in the axicabtagene ciloleucel arm, anti-CD19 CAR T levels measured in peripheral blood will be summarized with descriptive statistics.

### 10.6.7. Immunogenicity Analyses

The subject incidence of antibodies to axicabtagene ciloleucel will be summarized.

### 10.6.8. Health-related Quality of Life

Changes in EORTC QLQ-C30 domains and the EQ-5D-5L index and VAS scores from screening to the Month 24 post-randomization visit will be summarized with descriptive statistics. The WPAI will be scored per the instrument development algorithm (http://www.reillyassociates.net/WPAI_Scoring.html). Changes in the WPAI score from screening to Month 24 post-randomization visit will be summarized with descriptive statistics. In addition, the mean/median changes in EORTC QLQ-C30 domains, the EQ-5D-5L index, VAS scores, and WPAI score from screening over time will be present with plots.

### 10.6.9. Cytokines, Product Characteristics, and Molecular and Histological Characteristics

Among subjects in the axicabtagene ciloleucel arm, summaries of cytokines over time will be provided.

The proportions of cell phenotypes in the axicabtagene ciloleucel product will be summarized.

Analyses of tumor molecular and histologic characteristics by levels of PD-L1, and molecular and cytogenetic subclassifications will be summarized in the statistical analysis plan.

### 10.6.10. Long-term Data Analysis

All subjects who received at least one dose of axicabtagene ciloleucel as protocol therapy will be followed for survival for up to approximately 15 years after randomization; LTFU assessment will be performed on subjects after transition to the LTFU study (refer to Section 3.5.2 and Section 3.5.3). No formal hypothesis testing will be performed based on data obtained after the primary analysis of OS. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

# 11. REGULATORY OBLIGATIONS

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

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

## 11.1. Independent Review Board/Independent Ethics Committee

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

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study according to applicable law. 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 maintained for all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number.
- 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 year of birth (as per their local reporting requirements for both initials and year of birth).

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

## 11.3. Investigator Signatory Obligations

Each clinical study report will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma 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 Sponsor and Investigator Signature Page 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 its sole discretion, to determine whether to manufacture axicabtagene ciloleucel and provide it 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
- Essential documents for the conduct of this clinical study (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. If storage is no longer available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to shipping the documents.

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

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

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

# 14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contacts, 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 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, for compliance with protocol requirements as well as ICH/GCP, and applicable local regulations.

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

# 15. PUBLICATION

Authorship of publications from data generated in ZUMA-7 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states authorship should be based on:

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

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

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

Any publication, in any form, that is derived from this study must be submitted to Kite 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. Sponsor and Investigator Signature Page

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

### STUDY ACKNOWLEDGMENT

A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)

Amendment 6, 14 April 2023

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

PPD
Kite Medical Monitor Name (Printed)

*[Refer to the appended electronic signature]*
Signature

*[Refer to the appended electronic signature]*
Date

### INVESTIGATOR STATEMENT

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

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

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

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

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

Principal Investigator Name (Printed)

Signature

Date

Study Site Number

## Appendix B. Lugano Classification {Cheson 2014}

Please refer to imaging manual and {Cheson 2014} for details of assessment.

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

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

### Complete Remission:

***Complete Metabolic Response (CMR) for PET-CT-Based Response***

The designation of CMR requires all of the following:

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

***Complete Radiologic Response (CRR) for CT-Based Response***

The designation of CRR requires all of the following:

- Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion (LDi)
- No extralymphatic sites of disease
- Absent nonmeasured lesion
- Organ enlargement regress to normal

- No new sites of disease should be observed.
- Bone marrow normal by morphology; if indeterminate, IHC negative

**Partial Remission:**

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

The designation of PMR requires all of the following:

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

  Note:

  — At interim, these findings suggest responding disease.

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

- No new sites of disease should be observed.
- Residual uptake higher than uptake in normal bone marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed).

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

Partial Radiologic Response (PRR) for CT-Based Response

The designation of PRR requires all of the following:

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

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

  — When no longer visible, 0 x 0 mm

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

- Absent/normal, regressed, but no increase of nonmeasured lesions.
- Spleen must have regressed by > 50% in length beyond normal
- No new sites of disease should be observed.

**SD:**

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

The designation of NMR requires all of the following:

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

***Stable Radiologic Disease (SRD) for CT-Based Response***

The designation of SRD requires all of the following:

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

**PD:**

***Progressive Metabolic Disease (PMD) for PET-CT Based Response***

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

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

***Progressive Radiologic Disease (PRD) for CT- Based Response***

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

- An individual node/lesion must be abnormal with:
  - Longest traverse diameter (LDi) > 1.5 cm and

- Increase by ≥ 50% from cross product of LDi and perpendicular diameter (PPD) nadir and
- An increase in LDi or SDi, shortest axis perpendicular to the LDi, (SDi) from nadir
  - 0.5 cm for lesions ≤ 2 cm
  - 1.0 cm for lesions > 2 cm
- In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline;
- New or recurrent splenomegaly

- New or clear progression of preexisting nonmeasured lesions
- New lesion
  - Regrowth of previously resolved lesions
  - A new node > 1.5 cm in any axis
  - A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
  - Assessable disease of any size unequivocally attributable to lymphoma
- New or recurrent bone marrow involvement

# Appendix C. Patient Reported Outcomes

## EORTC QLQ C-30

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

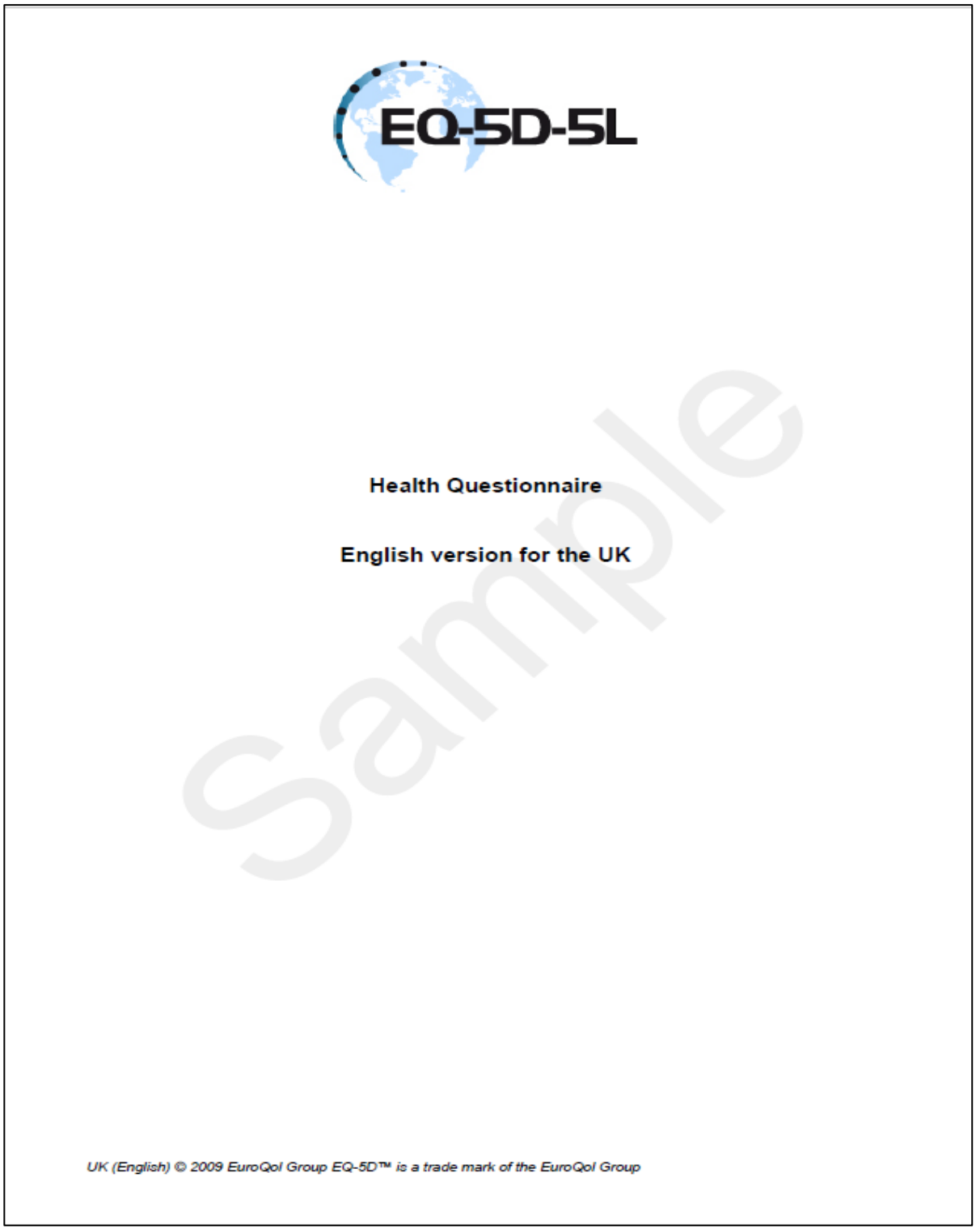
29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

**EQ-5D-5L**


EQ-5D-5L
Health Questionnaire
English version for the UK
Sample
UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

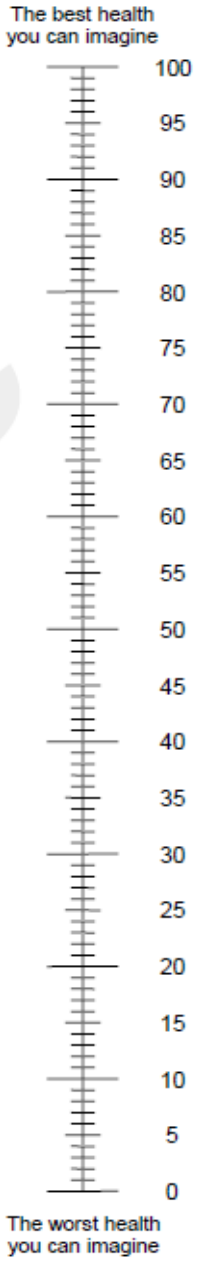
**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐






3

## WPAI Questionnaire (V2.0) (SAMPLE)

**Work Productivity and Activity Impairment Questionnaire:**
**General Health V2.0 (WPAI:GH)**

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   *If NO, check "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

WPAI:GH V2.0 (US English) 1

5. During the past seven days, how much did your health problems affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.*

Consider only how much health problems affected productivity while you were working.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Health problems had no effect on my work | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Health problems completely prevented me from working |

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.*

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Health problems had no effect on my daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Health problems completely prevented me from doing my daily activities |

CIRCLE A NUMBER

# Appendix D. Country-specific Regulatory Agency Requirements

## Germany and Switzerland

| Protocol Section | Country-specific Requirement |
|---|---|
| Section 7.6<br>Section 7.7<br>Section 7.9<br>Section 7.11.1 | 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 2, 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.<br>The daily monitoring will include vital signs (see Section 7.6), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11.1), and neurological assessment (which may include MMSE [see Section 7.7]). Any observed toxicity will be evaluated according to Section 7.9 of this protocol and managed according to the IB. |

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; IP, investigational product; MMSE, Mini-Mental Status Examination.

## France

| Protocol Section | Country-specific Requirement |
|---|---|
| Section 7.6<br>Section 7.7<br>Section 7.9<br>Section 7.11.1 | 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 2, column "IP administration period, 1-7." The ANSM recommends a 10-day hospitalization after infusion of any CAR T-cell product.<br>The daily monitoring will include vital signs (see Section 7.6), blood draw for chemistry panel with CRP, blood draw for CBC w/differential (see Section 7.11.1), and neurological assessment (which may include MMSE [see Section 7.7]). Any observed toxicity will be evaluated according to Section 7.9 of this protocol and managed according to the IB. |

Abbreviations: ANSM, National Agency for the Safety of Medicines and Health Products; CAR, chimeric antigen receptor; CBC, complete blood count; CRP, C-reactive protein; IP, investigational product; MMSE, Mini-Mental Status Examination.

## Switzerland

| Protocol Section | Country-specific Requirement |
|---|---|
| Section 5.2 | The additional exclusion criterion, applicable to Switzerland only, specifies the excipients of the CryoStor used in the cryopreservation of CAR T cells and frequently for $CD34^+$ stem cells, and is as follows:<br>History of severe immediate hypersensitivity reaction to tocilizumab or any of the agents used in this study, including the excipients DMSO and Dextran 40 present in CryoStor. |

Abbreviations: CAR, chimeric antigen receptor; DMSO, dimethyl sulfoxide.

## Sweden

| Protocol Section | Country-specific Requirement |
|---|---|
| N/A | **1. RISK AND BENEFIT ASSESSMENT**<br><br>Kite Pharma is conducting a global Phase 3, randomized, open-label study to evaluate the efficacy of axicabtagene ciloleucel versus standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma (Protocol number KTE-C19-107 [ZUMA-7]).<br><br>**1.1. Important Identified and Potential Risks related to IMP**<br><br>The risks of axicabtagene ciloleucel/KTE-C19 therapy are well described. Two important identified risks, which are not commonly encountered in general oncology practice, include CRS and neurologic events. These events have an early onset, generally within 1 week after the therapy, and are mostly reversible (> 95%). Additional important identified risks include cytopenias, infection and hypogammaglobulinemia. Strategies have been developed to monitor for and manage these Adverse Events (AEs) and are included in the most recent version of the Investigator Brochure (IB). The important potential risks associated with axicabtagene ciloleucel/KTE-C19 are replication competent retrovirus (RCR), secondary malignancy, autoimmune disorders reactivation/new onset, immunogenicity and tumor lysis syndrome (TLS).<br><br>**1.2. Mitigation of IMP-related risks**<br><br>**1.2.1. Subject selection (inclusion/exclusion criteria)**<br><br>The inclusion and exclusion criteria described in section 5 of the protocol ensure patients most at risk with regards to the identified important and potential risks associated with axicabtagene ciloleucel are not included in the study.<br><br>Inclusion criteria:<br><br>• 106. No known history or suspicion of central nervous system (CNS) involvement by lymphoma<br>• 110. Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as:<br>o Absolute neutrophil count (ANC) ≥1000/μL<br>o Platelet count ≥ 75,000/μL<br>o Absolute lymphocyte count ≥ 100/μL<br>o Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings<br>o Baseline oxygen saturation > 92% on room air<br><br>Exclusion criteria:<br><br>• 208. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides |

| Protocol Section | Country-specific Requirement |
|---|---|
| | • 209. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management. Simple urinary tract infection (UTI) and uncomplicated bacterial pharyngitis are permitted if responding to active treatment.<br>• 213. Subjects with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases<br>• 214. History or presence of non-malignant CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement<br>• 218. History of autoimmune disease, requiring systemic immunosuppression and/or systemic disease modifying agents within the last 2 years.<br><br>**1.2.2. Subject Monitoring**<br><br>All subjects will receive axicabtagene ciloleucel infusion at a health care facility, followed by daily monitoring at a health care facility for at least 7 days to monitor for signs and symptoms of CRS and neurologic events. Alternatively, subjects may be hospitalized to receive their axicabtagene ciloleucel infusion and be observed for CRS and neurologic events in the hospital setting, if deemed appropriate by the investigator.<br><br>If subjects are hospitalized, subjects should not be discharged from the hospital until all axicabtagene ciloleucel related non-hematological toxicities resolve to ≤ Grade 1 or return to baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain in a hospital for ongoing axicabtagene ciloleucel related fever, hypotension, hypoxia, or ongoing neurologic events > Grade 1, or if deemed necessary by the investigator. Subjects should be instructed to remain within proximity of the clinical study site for at least 4 weeks following axicabtagene ciloleucel infusion. Subjects and their family members/caregivers should be educated on potential CRS and neurologic symptoms such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, or tremor. Subjects or their family members/caregivers should be instructed to immediately contact the treating investigator or seek immediate medical attention if any of these symptoms develop.<br><br>*Toxicity management*<br><br>The goal of CRS management in anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is to prevent life-threatening conditions while preserving the benefits of antitumor effects. Carefully monitor subjects for signs and symptoms of CRS. |

| Protocol Section | Country-specific Requirement |
|---|---|
| | The CRS grading scale and a CRS management algorithm are provided in section 6.5 of the Investigator's Brochure to direct the investigators. This CRS management strategy is based on the experience to date with axicabtagene ciloleucel/KTE-C19 in addition to other anti-CD19 CAR T-cell products (Lee et al, 2014).<br><br>Carefully monitor subjects for signs and symptoms of neurologic events. Rule out other causes of neurologic symptoms. The neurologic events management algorithm is provided in section 6.5 of the investigator's brochure. This neurologic event management strategy is based on the experience to date with axicabtagene ciloleucel/KTE-C19 in addition to other anti-CD19 CAR T-cell products (Brudno and Kochenderfer 2016).<br><br>**1.3. Benefit-Risk Analysis**<br><br>Patients with r/r DLBCL especially primary refractory and early relapse within 1 year of firstline rituximab-based chemoimmunotherapy have poor prognosis even with high-dose therapy-autologous stem cell transplant (HDT-ASCT). Because these patients likely are resistant to chemotherapy, they may benefit from therapies with different mechanisms of action. 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 bi-specific T-cell engagers 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. Chimeric antigen receptor (CAR) engineered T-cells may address these issues and are a promising approach for cancer therapy.<br>Axicabtagene ciloleucel is an engineered autologous T-cell immunotherapy by which a patient's own T cells are collected and subsequently genetically altered to recognize CD19. CD19 is expressed on the cell surface of B-cell malignancies. In ZUMA-1, which investigated the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL, axicabtagene ciloleucel significantly improved ORR ($P < 0.0001$) compared to historical control. The ORR was 83% with a complete response (CR) rate of 58%. With a median follow up of 27.1 months, 39% of subjects had ongoing responses (37% in CR). 76% of patients in ZUMA-1 were refractory to 2$^{nd}$ or later line of therapy and 23% had an early relapse after ASCT. AEs, which can be severe or occasionally life-threatening, were well defined, generally reversible, and manageable, with no apparent long-term consequences other than B-cell aplasia. The most common events were cytopenias, which are expected from the conditioning chemotherapy, as well as CRS and neurologic events. The rates of severe CRS and neurologic events decreased over the course of the ZUMA-1 study, whereas efficacy remained consistent. In an analysis of data from the PARMA and CORAL trial the ORR to salvage therapy in less heavily pretreated patients with an early relapse after 1st line chemoimmunotherapy was only 40% and 46% respectively (Guglielmi et al, 1998) (Gisselbrecht et al, 2010). Axicabtagene |

| Protocol Section | Country-specific Requirement |
|---|---|
| | ciloleucel may even have a further improved efficacy and tolerability in this patient population with less chemo-refractory disease and lower disease burden. Therefore axicabtagene ciloleucel will be compared to standard of care (SOC) as 2nd line therapy in patients with chemo-refractory DLBCL or an early relapse after 1st line chemoimmunotherapy in the proposed ZUMA-7 study.<br>**1.4. Conclusion**<br>Treatment of patients with r/r DLBCL remains challenging and there is a significant unmet need for better therapies in these patients. This patient population has a specifically poor prognosis even with HDT-ASCT.<br><br>ZUMA-7 is a randomized and controlled study against standard of care as determined by the investigator based on guidance from the protocol. This design is expected to allow for appropriate assessment of the benefit of axicabtagene ciloleucel in patients with r/r DLBCL compared to current standard of care treatment, while maintaining an acceptable safety profile for the important identified risks of CRS, neurologic events, cytopenias, infections and hypogammaglobulinemia.<br><br>**2. SPONSOR REPORTING REQUIREMENTS**<br>Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Kite may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), the sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.<br><br>Assessment of expectedness for SAEs will be determined by Kite using reference safety information specified in the investigator's brochure or relevant local label as applicable.<br><br>All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.<br><br>**3. CONTACT PERSON FOR MEDICAL AND SAFETY QUERIES**<br>Investigators can contact the European medical monitor for medical and safety queries: |

| Protocol Section | Country-specific Requirement |
|---|---|
| | European Medical Monitor<br>PPD<br>Executive Director, Clinical Development<br>Mobile Phone: PPD<br>Email: PPD<br><br>Urgent Safety Issues Contact<br>PPD<br>Vice President Pharmacovigilance and Epidemiology<br>EU QPPV<br>Phone: PPD<br>Email: PPD<br><br>Adverse event and SUSAR reporting<br>Safety_FC@gilead.com<br><br>Relevant SAEs will be reported to MPA by the sponsor in accordance with local requirements. This includes SUSARs from all applicable trial sites.<br><br>**4. STUDY DISCONTINUATION**<br><br>Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Kite and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.<br><br>**5. REFERENCES**<br><br>Brudno JN, Kochenderfer JN. Toxicities of Chimeric Antigen Receptor T Cells: Recognition and Management. Blood. 2016;127(26):3321-30.<br>Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.<br>Guglielmi C, Gomez F, Philip T, Hagenbeek A, Martelli M, Sebban C, et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial. J Clin Oncol. 1998;16(10):3264-9.<br>Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95. |

## Appendix E. Childbearing Potential and Birth Control

This study will follow the recommendations from the Clinical Trials Facilitation Group (CTFG) {Clinical Trials Facilitation and Coordination Group (CTFG) 2020}, as described below.

1. Definition of Childbearing Potential

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

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

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

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

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Injectable
  - Implantable[a]
- Intrauterine device (IUD)[a]

[a] Contraception methods that in the context of this guidance are considered to have low user dependency.

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

3. Unacceptable Birth Control Methods

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

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

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

## Appendix F. Pandemic Risk Assessment and Mitigation Plan

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

These risks can be summarized as follows:

1) Subject safety monitoring and follow-up:

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

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

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

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

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

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

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

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

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

the local ethics committee/institutional review board. The consent process will be documented and confirmed by normal consent procedure at the investigative site at the earliest opportunity.

2) Protocol and monitoring compliance:

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

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

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

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

3) Missing data and data integrity:

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

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

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

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

## Appendix G. Protocol Amendment History

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

Earlier separate summaries of changes are available upon request.

A separate tracked change (red-lined) document comparing the previous protocol version (Amendment 5, dated 25 June 2020) and USA country-specific version (Amendment 5.1, dated 16 September 2020) to this amendment will be made available upon the publication of this protocol.

- **Amendment 6 (Dated 14 April 2023)**

- Changes from Amendment 5 (dated 25 June 2020) to Amendment 6 (dated 14 April 2023) are detailed below:

| Section Number and Name | High-level Description of Change | Brief Rationale |
|---|---|---|
| Title Page<br>Section 7.15 Long-term Follow-up (Axicabtagene Ciloleucel and Standard of Care Arms)<br>Section 8 Subject Withdrawal<br>Section 13 Study Documentation and Archive<br>Section 18, Appendix A: Sponsor and Investigator Signature Page<br>Section 18, Appendix E: Childbearing Potential and Birth Control | Minor administrative changes have been made throughout the protocol to align with Kite's latest protocol template. | To align with Kite's latest recommendations and processes |
| Protocol Synopsis<br>Study Schema<br>Section 3.5 Duration of Study and Subject Participation<br>Section 7.11.2.2 RCR Testing<br>Section 7.15 Long-term Follow-up (Axicabtagene Ciloleucel and Standard of Care Arms)<br>Table 4 Schedule of Assessment Long-term Follow-up Period | Clarification provided regarding study duration, visit frequency, and assessments for subjects randomized to the SOC and axicabtagene ciloleucel arms.<br>Additional updates included to clarify the transition of subjects to the separate LTFU study. | For clarification |
| Protocol Synopsis, Statistical Considerations section<br>Section 10.2.1 Study Endpoints Primary | Reference to an acceptable lower limit for the observed total EFS events to trigger the primary analysis has been removed at the request of the regulatory agency.<br>Additional minor changes made for alignment of language in protocol | Requested by a regulatory agency |

| Section Number and Name | High-level Description of Change | Brief Rationale |
|---|---|---|
| Section 10.3 Sample Size Considerations<br>Section 10.6 Planned Method of Analysis | amendments 5 25 June 2020 and 5.1 16 September 2020. | |
| Section 6.2.4.7 Axicabtagene Ciloleucel Retreatment | Retreatment eligibility criteria updated to reflect the maximum time after the initial axicabtagene ciloleucel infusion a subject can be retreated. | For clarification |
| Section 9.4 Reporting of Serious Adverse Events | Safety reporting email updated to: Safety_FC@gilead.com. Clarification added regarding any relevant information on ongoing SAEs post the database closure, which must be submitted to Kite within 24 hours after the investigator's knowledge of the event. | For clarification |
| Section 10.6.6 Pharmacokinetic Analyses | Anti-CD19 CAR T levels measured in peripheral blood will be summarized with descriptive statistics. | For clarification |
| Section 18 Appendix D Country-specific Regulatory Agency Requirements<br>Section 5.2 Exclusion Criterion # 222 | Country specific requirements added from separate documents for harmonization of the protocol to prepare for the EU CTR transition. | Requested by a regulatory agency |
| Section 18 Appendix F Pandemic Risk Assessment and Mitigation Plan | Addition of an appendix providing guidelines around pandemic risk assessments and mitigation plan. | Added for site guidelines around pandemic risk assessment. |
| Section 18 Appendix G Protocol Amendment History | Addition of an appendix (Protocol Amendment History added) presenting a high-level summary of changes for the amendment. | Addition to reflect Protocol Amendment 6 changes. |

## amd-6-prot-KTE-C19-107_final draft

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | Clinical Development eSigned | PPD |