STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	Axicabtagene Ciloleucel (KTE-C19)
Protocol:	A PHASE 2 OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL CONCOMITANT WITH PROPHYLACTIC STEROIDS IN SUBJECTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA IN THE OUTPATIENT SETTING
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADaM	analysis data model
AE	adverse event
AESI	adverse event of special interest
CAR	chimeric antigen receptor
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CTCAE	common terminology criteria for adverse event
eCRF	electronic case report form
EFS	event-free survival
EQ-5D-5L	European Quality of Life 5- Dimension 5-Level Scale
GVHD	Graft-Versus-Host-Disease
ICF	informed consent form
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWG	International Working Group
LBCL	large B cell lymphoma
LTFU	long term follow up
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	mini mental status exam
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PD	progressive disease
PR	partial response
RCR	replication-competent retrovirus
RCL	replication-competent lentivirus
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplant
SD	stable disease
SDTM	study data tabulation model
SOP	Standard Operating Procedures
SRT	safety review team
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides the specification and details for the statistical analyses to support the protocol KT-US-482-0137 (ZUMA-24) [Original version] entitled "A phase 2 open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel concomitant with prophylactic steroids in subjects with relapsed or refractory large b-cell lymphoma in the outpatient setting" dated 18FEB2022. The scope of this plan includes the interim, primary, and final analyses.

The pharmacokinetics/pharmacodynamics analysis will be described in a separate document (ie, translational SAP).

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the rate and severity of cytokine release syndrome (CRS) and neurologic events following outpatient administration of axicabtagene ciloleucel.

2.1.2. Secondary Objectives

- Characterization of the expanded safety profile including, time to onset and duration of CRS/neurologic events, time to hospitalization and ICU, incidence and duration of infections/cytopenias.
- Change in the European Quality of Life 5- Dimension 5-Level Scale (EQ-5D-5L) over time over time.
- Assessment of clinical efficacy.
- Assessment of pharmacokinetics and pharmacodynamics, including levels of anti-CD19 CAR-T cells and serum proinflammatory, immuno-modulatory and effector molecules.

2.1.3. Exploratory Objectives

- Explore the pattern of worsening of CRS and neurological events following axicabtagene ciloleucel administration (ie, time from Grade 1 to Grade 2).
- Exploration of the utility of electronic wearable technology in outpatient monitoring and assessment of predictive modeling for outpatient selection for axicabtagene ciloleucel treatment
- Assessment of T-cell immunogenicity against the chimeric antigen receptor (CAR).

2.2. Endpoints

2.2.1. Primary endpoint

Incidence rate and severity of CRS and neurologic events.

2.2.2. Secondary Endpoints

- Time to onset and duration of CRS and neurologic events following axicabtagene ciloleucel administration.
- Rates of hospitalization after axicabtagene ciloleucel infusion as measured by proportion of hospitalized subjects within 72 hours, 7 days, 14 days, and 30 days.

- Duration of initial hospitalization after axicabtagene ciloleucel infusion.
- Proportion of ICU admitted subjects.
- Duration of ICU admission during first hospitalization after axicabtagene ciloleucel infusion.
- Safety of axicabtagene ciloleucel as measured by the incidence of adverse events (AE)s and serious adverse events (SAEs).
- Change of EQ5D-5L from Baseline to Month 6.
- Efficacy of axicabtagene ciloleucel as measured by overall response rate (ORR), complete response (CR) rate, duration of response (DOR), progression-free survival (PFS), event-free survival (EFS) (all per investigator assessment), and overall survival (OS).
- Blood levels of key serum analytes (including cytokines), and axicabtagene ciloleucel CAR T-cells over time

2.2.3. Exploratory Endpoints

- Time from end of axicabtagene ciloleucel infusion to:
  - Initial and subsequent CRS, and progression to higher grade CRS
  - Initial neurologic events, and progression to higher grade neurologic events
  - Tocilizumab administration
  - Corticosteroid administration (aside from prophylactic dexamethasone per protocol)
  - Administration of vasopressors
  - Administration of supplemental oxygen for documented hypoxemia
- Number of urgent care/emergency department visits and/or unscheduled outpatient visits with/without subsequent hospital admission
- Cumulative use of corticosteroids and other concomitant medications of interest
- Phenotypes and functional attributes of pre-infusion axicabtagene ciloleucel (product characterization)
- Incidence of anti-T-cell immunogenicity
- Extended characterization of serum and plasma analytes and association with clinical outcome

The analysis on secondary and exploratory endpoints for pharmacokinetics/pharmacodynamics will be described in the translational SAP.

3. STUDY DESIGN

3.1. Overview

This is a Phase 2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with r/r LBCL in the outpatient setting.

Approximately 40 subjects will be enrolled in this Phase 2 study.

The 28-day screening period begins on the date the subject signs the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) and continues through confirmation of enrollment (ie, commencement of leukapheresis), or until the subject withdraws consent before enrollment, or it is determined that the subject is a screen failure. Study sites will maintain a log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information such as the date of screening, date the subject was enrolled, or the reason why the subject failed screening. These data will be entered in the electronic case report form (eCRF).

Informed consent must be obtained before completion of any nonstandard-of-care, study-specific procedures. Procedures that are part of the standard of care are not considered study-specific procedures and may be performed before obtaining consent and used to confirm eligibility.

A subject is considered enrolled in the study at commencement of leukapheresis. Subjects must have undergone screening procedures and their results must have been confirmed to meet the study eligibility criteria at screening. For laboratory tests performed after screening and before initiation of leukapheresis, allowance will be made for expected normal variation of within 5% of laboratory test value cutoffs noted in the inclusion criteria. If there is a need for a subject to have leukapheresis repeated, they must continue to meet the study eligibility criteria (or within 5% of the laboratory test value cutoffs noted in the inclusion criteria) before the leukapheresis procedure is performed.

After enrollment/leukapheresis, subjects may undergo optional bridging therapy at investigator discretion.

After enrollment/leukapheresis and before initiation of lymphodepleting (conditioning) chemotherapy, subjects and family caregivers are required to be educated on taking vital signs in an outpatient setting, symptoms and signs of CRS and neurologic events, and the outpatient monitoring schedule.

Subjects will then undergo conditioning/lymphodepleting chemotherapy with fludarabine 30mg/m^2 and cyclophosphamide 500mg/m^2 for 3 consecutive days from Day −5 to Day −3, followed by prophylactic corticosteroid treatment with 10 mg dexamethasone, administered daily on Day 0, Day 1, and Day 2.

On Day 0 (following dexamethasone 10 mg), all subjects will receive a single infusion of axicabtagene ciloleucel at the target dose of 2 X 10^6 cells/kg without being hospitalized. Subjects will stay in a close vicinity to the clinic with immediate access to care by the investigator and/or the treating team.

After completing the axicabtagene ciloleucel infusion, all subjects will be followed in the outpatient setting for 14 days during the post-treatment assessment period. Starting from Day 0 (the day of axicabtagene ciloleucel infusion), subjects will return to the clinic for evaluation at Week 4, Month 2, and Month 3.

Upon completion of the post-treatment assessment period, subjects will enter the long term follow up (LTFU) period. Subjects who complete a minimum of 24 months of follow up may be transitioned to a LTFU study (KT-US-982-5968).

3.2. Statistical Hypothesis

No formal hypothesis will be tested. All analyses will be descriptive.

3.3. Sample Size Consideration

This study uses an open-label, single-arm design, with a planned sample size of approximately 40 subjects.

3.4. Statistical Assumptions

The independence of subject responses will be assumed.

4. COVARIATES

4.1. Covariates

The following baseline covariates may be used to examine the efficacy and/or safety in subgroup or covariate analyses.

- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0, 1)
- Age (in years) at baseline (< 65, ≥ 65)
- Sex (male, female)
- Disease type
- Prior lines of therapy (2 vs 3+)
- Disease stage

Covariate levels that are sparse may be collapsed for purposes of statistical modeling. Additional associative analyses of covariates with subject outcomes may be explored.

5. DEFINITIONS

5.1. General

Study enrollment date: Study enrollment date is defined as the day when a subject commences leukapheresis.

Study Day 0: Study Day 0 is defined as the day the subject received the first axicabtagene ciloleucel infusion. The day before Study Day 0 will be Study Day −1. The day of enrollment and any days after enrollment and before Study Day −1 will be sequential and negative integer-valued.

Baseline: The baseline value is defined as the last non-missing value taken prior to conditioning chemotherapy. For subjects without conditioning chemotherapy date, the baseline value is taken as the last non-missing value on the study.

Retreatment period: (defined only for subjects who undergo retreatment with axicabtagene ciloleucel): the retreatment period starts on the earliest date of the re-leukapheresis, the lymphodepleting chemotherapy for retreatment, and the retreatment of axicabtagene ciloleucel.

Retreatment baseline: Baseline for retreatment is defined as the last assessment taken before the earliest of the re-leukapheresis, the lymphodepleting chemotherapy for retreatment, and the retreatment of axicabtagene ciloleucel.

Actual follow-up time: Actual follow-up time among all subjects treated with axicabtagene ciloleucel is calculated as the time from the first infusion of axicabtagene ciloleucel to the date of death or last date known to be alive, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the first infusion of axicabtagene ciloleucel to the data cutoff date for the analysis.

Study therapy: Study therapy includes bridging chemotherapy, conditioning chemotherapy and axicabtagene ciloleucel infusion.

On-study: Time from enrollment to the last date of contact or death.

5.2. Safety

Treatment-emergent adverse event (TEAE): Any adverse event with onset on or after the axicabtagene ciloleucel infusion. AE, SAE and death reporting requirements are specified in protocol KT-US-482-0137 Section 7.5.

Deaths: All deaths that occur from enrollment up through the end of study will be summarized. Deaths that occur from the first infusion of axicabtagene ciloleucel up through 3 months after the infusion will also be summarized.

Time to onset of an AE of interest: The time from the date of the first axicabtagene ciloleucel infusion until the earliest date of onset of the AE in the event class of interest, using the following equation: the start date of the first AE in the event class – the date of the first axicabtagene ciloleucel infusion + 1.

Duration of an AE of interest: The time from the earliest onset date of the AE in the event class of interest until the resolution date of the last AE in the event class, regardless of any gaps occurring between events, using the following equation: the resolution date of the last AE in the event class – the start date of the first AE in the event class + 1. The duration of an AE of interest may only be calculated for a subject if all AEs in the event class encompassing the AE of interest have resolved by the data cutoff date.

CRS: CRS as a syndrome (ie, a collection of individual symptoms) is identified via collection of the syndrome on a case report form specifically designed to collect CRS. Individual symptoms of CRS are separately collected on the AE log and are linked to the CRS syndrome. CRS syndrome severity is graded according to a modification of the grading system proposed by Lee {Lee 2014}. In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome; rather, they are reported on the AE log form separately based on specific symptoms per Common Terminology Criteria for Adverse Events (CTCAE).

Neurologic Events: Neurological AEs are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. The search strategy focuses on central nervous system toxicity, without regard to temporal relationship and concomitant conditions (eg, CRS). Additionally, the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs. Neurologic toxicity will be reported separately from CRS.

AEs of special interest: Adverse events of special interest (AESI) for axicabtagene ciloleucel treatment include AEs in the following categories:

Important identified risks other than CRS and neurological events:

1) Cytopenias: Cytopenias (thrombocytopenia, neutropenia, or anemia) will be identified as follows:

    a) Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search)

    b) Neutropenia is identified using a MST search strategy defined by Kite

    c) Anemia (including aplastic anemia) is identified using the SMQ haematopoietic erythropenia (broad search)

2) Infections: Infections are identified as AEs within the system organ class of infections and infestations that occur on or after the axicabtagene ciloleucel infusion, in MedDRA SMQ of opportunistic infections (narrow search), and in MedDRA high level group terms (HLGT) that capture events of:

    a) Bacterial infection, encompassing preferred terms within the MedDRA HLGTs of

        i) Bacterial infectious disorders

        ii) Chlamydial infectious disorders

    b) Viral infection, encompassing preferred terms within the MedDRA HLGT of viral infectious disorders

    c) Other infections, encompassing preferred terms within the MedDRA HLGT of infections - pathogen unspecified.

3) Hypogammaglobulinemia: Hypogammaglobulinemia will be identified using a MST search strategy defined by Kite.

Important potential risks:

1) Secondary malignancies: AEs coded within the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) and deaths will be reviewed by the Kite Safety and Pharmacovigilance Team for potential secondary malignancies.

2) Immunogenicity (anti-axicabtagene ciloleucel antibodies): Subjects will be tested for the development of antibodies by testing for reactivity against FMC63, the parent murine antibody used for the development of the single-chain variable region fragment (scFv) of the anti-CD19 CAR construct. Positive samples will then be tested to confirm the presence of antibody to the extracellular portions of anti-CD19 CAR.

3) Replication competent retrovirus (RCR): Since anti-CD19 CAR T cells comprise gamma murine retroviral vector-transduced T cells, the presence of RCR in the blood of treated subjects will be monitored.

4) Tumor lysis syndrome: Tumor lysis syndrome will be identified using the SMQ of tumor lysis syndrome. The narrow version of this SMQ will be used.

5) Aggravation of Graft-Versus-Host-Disease (GVHD): GVHD will be identified using a MST search strategy defined by Kite that uses preferred term subsets from the HLGT of procedural related injuries and complications not elsewhere classified (NEC) and high-level term (HLT) of immune and associated conditions NEC. Aggravation of GVHD will comprise those events which are of new onset or have worsened by one or more CTCAE grades since study entry.

Other AESIs:

1) Cardiac failure: Cardiac failure will be identified using the SMQ of cardiac failure. The narrow version of this SMQ will be used.

2) Cardiac arrhythmias: Cardiac arrhythmias will be identified using the SMQ of cardiac arrhythmias. The narrow version of this SMQ with selected broad SMQ preferred terms will be used.

3) Autoimmune disorders: Autoimmune disorders will be identified using the SMQ of immune-mediated/autoimmune disorders. The narrow version of this SMQ will be used.

4) Bone marrow failure: Bone marrow failure will be identified using the narrow SMQ of haematopoietic cytopenias affecting more than one type of blood cell.

5.3. Efficacy

Objective Response Rate (ORR): ORR is defined as the proportion of subjects with either a complete response or a partial response by the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2014} as determined by the study investigators. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered nonresponders, including subjects with non-evaluable assessment data and those without any assessment. The derivation of this endpoint will only include the response assessments obtained after the initial axicabtagene ciloleucel infusion and up to PD or the disease assessments before any subsequent anticancer therapy (excluding SCT). A sensitivity analysis for ORR may be performed by including SCT as subsequent anticancer therapy.

CR Rate: CR rate is defined as the incidence of an investigator-assessed complete response by the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma {Cheson 2014} as determined by the study investigators.

Duration of Response (DOR): DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or, if no disease progression, death due to any cause. Response and progression are defined per investigator assessment per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014}. Subjects not meeting the criteria for progression or death due to any cause by the analysis cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing. Subjects who receive subsequent anticancer therapy (excluding SCT) without documented progression will have DOR censored at the last evaluable disease assessment before the commencement of the new anticancer therapy. A sensitivity analysis for DOR may be performed by including SCT as subsequent anticancer therapy.

Progression-free Survival (PFS): PFS is defined as the time from axicabtagene ciloleucel infusion date to the date of disease progression or, if no disease progression, the date of death due to any cause. Progression is defined per investigator read per the revised IWG Response

Criteria for Malignant Lymphoma {Cheson 2014}. Subjects not meeting the criteria for progression or death due to any cause by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive subsequent anticancer therapy (excluding SCT) without documented progression will have PFS censored at the last evaluable disease assessment before the commencement of the new anticancer therapy. A sensitivity analysis for PFS may be performed by including SCT as subsequent anticancer therapy.

Event Free Survival (EFS): EFS is defined as the time from axicabtagene ciloleucel infusion to the earliest date of disease progression, commencement of new anti-lymphoma therapy (excluding SCT), or death from any cause. Progression is defined per investigator read per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014}. Subjects not meeting the criteria for progression, not receiving any subsequent anti-lymphoma therapy and alive by the analysis data cutoff date will be censored at their last evaluable disease assessment date. A sensitivity analysis for EFS may be performed by including SCT as subsequent anticancer therapy, i.e. considering SCT as event.

Overall Survival (OS): OS is defined as the time from axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last contact date. A sensitivity analysis for OS may be performed by using Full Analysis Set, and OS is calculated from time of enrollment to the date of death from any cause.

6. ANALYSIS SETS

6.1. Full Analysis Set

The Full analysis set consists of all enrolled subjects. The full analysis set will be used for summaries of subject disposition.

6.2. Safety Analysis Set

The Safety Analysis Set consists of all subjects who were treated with any dose of axicabtagene ciloleucel.

6.3. Efficacy Evaluable Set

Efficacy endpoints will be based on efficacy evaluable set consisting of all subjects enrolled and treated with axicabtagene ciloleucel at a target dose of 2 $x10^6$ anti-CD19 CAR T cells/kg and who have documented disease at baseline and subsequent tumor assessment following axicabtagene ciloleucel infusion. The efficacy evaluable set will be used for all efficacy analyses unless otherwise specified.

6.4. Retreatment Analysis Set

The retreatment analysis set consists of all subjects who are retreated with any dose of axicabtagene ciloleucel. This set will be used for all retreatment efficacy and safety data listings.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

No formal interim analysis is planned for this phase 2 study, During the study, a Safety Review Team (SRT) will review the available composite safety after the first 6 subjects have been dosed and have had the opportunity to be followed for 14 days to analyze risk versus benefit. Enrollment will be paused when the sixth subject is dosed and resumed after this safety evaluation as detailed in the SRT charter. If no unacceptable safety risk due to outpatient dosing is identified, the enrollment will be resumed, and the study will continue with continuous real-time monitoring of safety outcomes.

In order to evaluate the feasibility of the outpatient approach and to inform the Sponsor's decision on whether to continue the study, the SRT will also perform a review when approximately 20 enrolled and treated subjects have been followed for at least 14 days after axicabtagene ciloleucel infusion. Enrollment will be paused when the 20th subject is dosed and resumed after this safety evaluation as detailed in the SRT charter.

Safety data will be under continuous monitoring.

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subjected to the edit checks outlined in the Data Management Plan and the additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock. For interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted for the snapshot.

8.2. Electronic Transfer and Archiving of Data

The database for this study will be a Medidata RAVE system, managed and maintained by Kite Pharma (hereafter referred to as Kite) or designee. Raw datasets, study data tabulation model (SDTM) datasets, and analysis data model (ADaM) datasets will be generated by Kite or designee and will be archived for all planned analyses. Any additional unplanned analyses that occur after the primary analyses and before the final analysis will also be archived. Key data external to the clinical study database will be included in the relevant SDTM and ADaM modules when the external data are available.

Data from the central pathology laboratory, the product characteristics, central laboratory assessment of subjects' samples (axicabtagene ciloleucel CAR T-cell levels in blood, antibody assays, replication-competent retrovirus/lentivirus [RCR/RCL] testing) and central radiology review, if applicable, will be generated from contract laboratories and Kite. These data will be transferred to Kite and held in a peripheral directory and not built into the clinical trial database. At the time these data are required for analyses, they may be merged with the SDTM and ADaM datasets.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

Every effort will be made to obtain the complete data. The method for handling missing or incomplete data is described in the definition for each efficacy endpoint. In the event of a partial or missing death date, the imputation rule and the corresponding censoring date for survival can be found in Appendix 1.

8.3.2. Safety

AE start dates that are missing or incomplete will be imputed, and the algorithm defined in Appendix 1 will be used. Death dates that are completely missing or that only include a year of death will not be imputed.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include, but not be limited to, violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessments of radiologic scans and disease assessments may be subject to bias.

8.5. Outliers

Descriptive statistics will be used to identify potential outliers in any key variable analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6. Validation and Configuration Management

Programs for the development of the SDTM and ADaM datasets and the generation of the tables, figures, and listings will be developed and maintained according to Kite and/or designee's Standard Operating Procedures (SOPs). The name and version of the software used to generate analyses will be specified in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

Two SRT reviews will be conducted when 6 and 20 subjects have been dosed and have had the opportunity to be followed for 14 days, respectively.

The primary analysis will be conducted when all enrolled and treated subjects have had the opportunity to be followed for 6 months after the infusion.

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

The final analysis will occur when all enrolled subjects have withdrawn from study, lost to follow up, died or rolled over to the LTFU study.

9.2. Subject Disposition

The number of subjects enrolled/leukapheresed, treated with bridging therapy, treated with conditioning chemotherapy, treated with axicabtagene ciloleucel, and retreated with axicabtagene ciloleucel will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized.

Summaries of actual and potential follow-up time among all subjects treated with axicabtagene ciloleucel will be provided.

The number of subjects enrolled by country and site will be summarized.

The number of subjects in each analysis set will be provided.

9.3. Important Protocol Deviations

The clinical study team will define important protocol deviation categories and review all potential important protocol deviations at minimum, before the database snapshot for the primary efficacy analysis. Important protocol deviations will be categorized by deviation type (eg entry eligibility, use of excluded medication). The subject incidence of important protocol deviations will be summarized overall and by deviation category.

9.4. Demographic and Baseline Characteristics

Summary statistics and frequencies for demographic and baseline characteristics as listed in Section 4.1 will be tabulated.

9.5. Efficacy Analyses

The primary efficacy analyses will be conducted on the efficacy evaluable analysis set.

The investigator reviewers will determine disease assessments per the revised IWG Response Criteria for Malignant Lymphoma {Cheson 2014}.

For subjects who receive retreatment with axicabtagene ciloleucel, disease assessments obtained prior to retreatment will be included in the primary summaries of ORR, EFS and PFS. Disease assessments obtained after retreatment may be included in the summaries of BOR, EFS and PFS during retreatment period. The subject's OS time will be derived from the last date the subject was known to be alive regardless of retreatment time.

In the event any subject undergoes any subsequent anticancer therapy (excluding SCT) while on study, the subject's best response will be derived based on disease assessments obtained before the initiation of the new therapy. A sensitivity analysis may be conducted in which the derivation of DOR, EFS and PFS for subjects who undergo SCT while in an axicabtagene ciloleucel induced response will exclude the disease assessments obtained after the SCT into consideration. (See details in Appendix 3).

9.5.1. ORR

The subject incidence of objective response rate (CR/PR) per investigator assessment will be calculated. 95% confidence intervals will be provided about the ORR, calculated with the Clopper-Pearson method (an exact interval).

9.5.2. CR Rate

The overall complete response rate (CR) per investigator assessment will be calculated. 95% confidence intervals will be provided about the CR, calculated with the Clopper-Pearson method (an exact interval).

9.5.3. DOR

The Kaplan-Meier approach will be used to estimate DOR. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for DOR per investigator assessment, respectively. The Kaplan-Meier estimates of median duration, event-free rate (i.e remained in the response) and their 2-sided 95% CIs will be generated. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

A sensitivity analysis of DOR may be conducted in which disease assessments obtained after SCT (for subjects who undergo SCT while in an axicabtagene ciloleucel induced response) are excluded in the derivation of DOR. DOR will be censored at the last disease assessment before SCT while in remission.

DOR might also be summarized by the best overall response of CR or PR.

9.5.4. PFS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and progression-free will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for PFS per investigator assessments.

A sensitivity analysis of PFS may be conducted in which disease assessments obtained after SCT are excluded in the derivation of PFS. PFS will be censored at the last disease assessment before SCT without documented progression.

PFS might also be summarized by the best overall response of CR, PR or non-responders.

9.5.5. EFS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for EFS. Estimates of the proportion of subjects alive and progression-free will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for EFS per investigator assessments.

A sensitivity analysis of EFS may be conducted in which disease assessments obtained after SCT are excluded in the derivation of EFS. Subjects will have an EFS event of SCT at the time of SCT.EFS might also be summarized by the best overall response of CR, PR or non-responders.

9.5.6. OS

The analysis of OS will use the same methods as the analysis of PFS.

A swim lane plot may be provided. The horizontal axis represents the actual follow-up time from the time of axicabtagene ciloleucel infusion while each lane represents a subject. On each lane, disease assessments, death, new anti-lymphoma therapies, SCT, re-treatment and EOS will be marked at the time when they occur.

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all AEs and laboratory values with an onset on or after the axicabtagene ciloleucel infusion date and before the retreatment period (if applicable). Additional summary tables may be provided to present the AEs that occurred within certain study periods. For subjects who undergo retreatment with axicabtagene ciloleucel, AEs occurring in the retreatment period may be presented separately by subject listings.

AEs will be coded with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the CTCAE version 5.0.

CRS will be graded using a revised CRS grading scale (see details in protocol) developed by Lee and colleagues {Lee 2014}. Individual symptoms associated with CRS will be graded per CTCAE version 5.0.

Fatal AEs that are attributed to disease progression may be included in the summary of deaths with a primary death reason being the primary disease regardless of the coded MedDRA preferred term.

Subjects enrolled but not dosed with axicabtagene ciloleucel will be followed for AEs for 30 days after the last study-specific procedure, or until initiation of a new anticancer therapy, whichever occurs first. AEs reported in these subjects will be archived in the study database and available in the SDTM and ADaM datasets, but will not be tabulated in AE summaries.

9.6.1. AEs

The subject incidence of the following TEAEs will be tabulated by preferred term and/or system organ class:

- All AEs
- All SAEs
- All axicabtagene ciloleucel -related TEAEs
- All axicabtagene ciloleucel-related SAEs
- All Grade 3 or higher TEAEs
- All Grade 3 or higher axicabtagene ciloleucel-related TEAEs
- Fatal TEAEs
- TEAEs of interest, including important identified risks, important potential risks and other AESIs specified in Section 5.2.

The subject incidence summary of deaths by time periods and a subject listing of deaths will be provided. The primary reasons of death will also be summarized.

Subgroup analyses of TEAEs may be generated for selected covariates from the list in Section 4.1.

Cytopenias will be summarized by categories of neutropenia, anemia, and thrombocytopenia; cytopenias present on or after 30 days from the axicabtagene ciloleucel infusion will also be summarized.

Infections will be summarized by categories (bacterial infections, viral infections, opportunistic infections, and other infections). Time to onset and duration of infection will be summarized using Kaplan-Meier estimates.

Potential new malignancies will be identified within the system organ class of neoplasms benign, malignant, and unspecified (including cysts and polyps). Potential new malignancies will be listed.

9.6.1.1. CRS

The subject incidence and severity of CRS will be tabulated by symptom preferred term.

Summary statistics for following endpoints will be provided using Kaplan-Meier estimates:

- Time to onset of initial CRS following axicabtagene ciloleucel administration
- Duration of CRS
- Number and proportion of subjects with worsened subsequent CRS (higher grade relative to initial CRS)
- Time from initial CRS onset to the next higher grade CRS

A stacked bar graph of CRS events by grade will be plotted by study day.

Listing will be provided for all CRS and their associated symptoms.

9.6.1.2. Neurologic Events

The subject incidence and severity of neurologic events will be tabulated by preferred term.

Summary statistics for following endpoints will be provided using Kaplan-Meier estimates:

- Time to onset of neurologic events following axicabtagene ciloleucel administration
- Duration of neurologic events
- Number and proportion of subjects with worsened subsequentneurologic events (higher grade relative to initial neurologic event)
- Time from initial neurologic event onset to the next higher grade neurologic event

A stacked bar graph of neurologic events by toxicity grade will be plotted by study day.

Listing will be provided for all neurologic events. A separate listing of grade≥ 3 neurologic events will also be provided.

9.6.2. Prior and Concomitant Medications

Concomitant medication is defined as the medications administered on or after the first axicabtagene ciloleucel infusion date.

The subject incidence of prior and concomitant medications will be provided and summarized by medication category and WHO drug coded term. The indication of concomitant medications of interest for systemic steroids, tocilizumab, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and intravenous immunoglobulins, defined by Kite, will be summarized.

Number of doses of steroids administered will be categorized and number of subjects in each category will be provided. Summary statistics will also be provided for cumulative systemic steroid dosage (cortisone equivalent dose will be used).

Listings will be provided for subjects who received systemic steroids and tocilizumab, and subjects who received supplemental oxygen for documented hypoxemia.

9.6.3. Laboratory Test Results

Laboratory results will be graded according to CTCAE version 5.0. The incidence of post-infusion worst-grade laboratory abnormalities for all laboratory test analytes will be provided. Additional summaries for the shift from before infusion to the worst toxicity grade after axicabtagene ciloleucel infusion may also be generated.

9.6.4. Anti-axicabtagene ciloleucel antibodies

The subject incidence of any antibodies to the axicabtagene ciloleucel will be tabulated. For subjects testing positive for antibodies, the persistence of the antibodies over time will be summarized and listed.

9.6.5. RCR

The subject incidence of RCR/RCL detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR/RCL over time will be summarized and listed.

9.6.6. Exposure to Study Treatment

Summary statistics and subject listings will be provided for the following:

- Total body surface area-adjusted dose of cyclophosphamide
- Total body surface area-adjusted dose of fludarabine
- Weight-adjusted dose of axicabtagene ciloleucel
- Total CAR T cells in the axicabtagene ciloleucel infusion
- Total T cells in the axicabtagene ciloleucel infusion

Separate summaries will be presented for retreatment with lymphodepleting chemotherapy and axicabtagene ciloleucel among subjects in the safety retreatment analysis set.

9.6.7. Concomitant Procedures

Concomitant procedure is defined as the procedure started on or after the first axicabtagene ciloleucel infusion date. The subject incidence of procedures will be tabulated. A listing of concomitant procedures will be provided. If its indication is AE, then the AE's information will also be included.

9.6.8. Mini Mental Status Exam (MMSE)

Summary statistics for the MMSE score and change from baseline in the MMSE score over time will be provided.

9.7. Patient-Reported Outcomes

EQ-5D-5L index and visual analog scale (VAS) scores will be summarized by scheduled visits. Changes in VAS scores from baseline to each post-baseline visit after the axicabtagene ciloleucel infusion will be summarized with descriptive statistics.

9.8. Product Characteristics

A subject listing of product characteristics will be provided. Please refer to the Translational SAP for details.

9.9. Pharmacokinetics

Please refer to the Translational SAP for details.

9.10. Pharmacodynamics

Please refer to the Translational SAP for details.

9.11. Prior and Subsequent Anti-Lymphoma Therapy

The incidence of prior and subsequent anticancer therapy (by WHO Drug coded term), including transplant, will be summarized.

9.12. Duration Metrics

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of lymphodepleting chemotherapy
- Days from leukapheresis to the axicabtagene ciloleucel product release

- Days from leukapheresis to delivery of the axicabtagene ciloleucel product at the study site
- Days from leukapheresis to administration of axicabtagene ciloleucel
- Days from lymphodepleting chemotherapy to administration of axicabtagene ciloleucel

9.13. Hospitalization

Rates of hospitalization due to SAE as measured by proportion of hospitalized subjects within 72 hours, 7 days, 14 days, and 30 days after axicabtagene ciloleucel infusion will be summarized.

Proportion of ICU admitted subjects in the safety analysis set within 72 hours, 7 days, 14 days, and 30 days after axicabtagene ciloleucel infusion will be summarized.

Descriptive statistics (number of subjects, mean, standard deviation, interquartile range, minimum and maximum) will be provided for duration of first hospitalization after axicabtagene ciloleucel infusion, and duration of ICU admission during first hospitalization after axicabtagene ciloleucel. Descriptive statistics will also be provided for time to hospitalization and/or ICU from axicabtagene ciloteucel infusion.

Number of urgent care/emergency department visits and/or unscheduled outpatient visits with/without subsequent hospital admission may be summarized if such data is available.

Listing will be provided for hospitalization and ICU use.

9.14. Electronic Wearable Devices

For research purpose, visualization may be provided for the fever episode data detected by the electronic wearable device.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes to protocol-specified analyses have been made.

11. REFERENCES

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12. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates and Time
Appendix 2. Last Date Known to Be Alive
Appendix 3. Derivation of Time to Event Endpoints

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates and Time

The following data will be imputed using the following algorithm:

- Adverse event (AE) dates
- Concomitant medication dates
- Subsequent anticancer therapy dates
- Death date (using algorithm 3)
- Infusion time (using algorithm 4)
- Hospitalization/ICU admission and discharge time (using algorithm 4)

1) Start dates imputation:

Table 1. Imputation Rules for Partial or Missing Start Dates

Start Date		If End Date is						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< Day 0	≥ Day 0	< Day 0 *yyyymm*	≥ Day 0 *yyyymm*	< Day 0 *yyyy*	≥ Day 0 *yyyy*	
Partial *yyyymm*	= Day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	= Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

Abbreviation: n/a, not applicable.
Note: If the start date imputation leads to a start date that is after the end date, then do not impute the start date.
1 = impute the date of Day 0.
2 = impute the first of the month.
3 = impute January 1 of the year.
4 = impute January 1 of the stop year.

2) End dates imputation:

   a) If start date is partial or missing, the start date will be imputed first.

   b) If year is missing or event is ongoing, the end date will not be imputed.

c) If year and month are available, but day is missing, set the end date to the last day of the month.

d) If year is available, but month is missing,

i) If day is not missing, set the month to December of the year.

ii) If day is missing, set the end date to December 31st of the year.

e) If the imputed end date is prior to the start date after imputation, set the end date to the last date known to be alive.

f) If the imputed end date is after the earliest non-missing date of data extract date, end of study date, and death date, set the end date to the earliest non-missing date of data extract date, end of study date, and death date.

g) If the imputed end date is after the data cut-off date when applicable, set the end date to missing and end relative to reference time point is set to "ONGOING". For as-is snapshot, this step can be omitted.

3) Imputation rules for partial or missing death dates:

a) If death year and month are available, but day is missing:

i) If mmyyyy for the last date known to be alive = mmyyyy for death date, set death date to the day after the last date known to be alive.

ii) If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.

iii) If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.

b) If both month and day are missing for death date or a death date is completely missing, do not impute, and censor the subject per censoring rules defined in Appendix 3.

4) When the time to hospitalization/ICU is to be computed and either time is missing, please follow the algorithm below.

a) If infusion time is missing, may it be partially missing or completely missing, then impute it to the last possible time permitted to the known part of time or 23:59:59 of the day.

b) If hospital/ICU admission time is missing, then impute it to the earliest possible time permitted to the known part of time or 00:00:00 of the day.

c) If hospital/ICU end time is missing, then impute it to the last possible time permitted to the known part of time or 23:59:59 of the day.

Appendix 2. Last Date Known to Be Alive

Last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE
- Leukapheresis dates
- Bridging therapy administration dates
- lymphodepleting chemotherapy administration dates
- anti-CD19 CAR T cells infusion dates
- Computerized tomography (CT) scan dates
- Positron emission tomography (PET) scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Other tumor assessment dates (Bone marrow and spleen assessments)
- Tumor tissue biopsy
- Disease response assessment
- Long-term follow-up subject status date
- End of treatment disposition where status is not equal to death, lost to follow-up
- End of study data where end of study reason is not equal to death, lost to follow-up
- Survival Status where status = alive
- Death date

If the last known alive date is after the cut-off date, set the last known alive date to the cut-off date.

Appendix 3. Derivation of Time to Event Endpoints

Additional details on the derivations of duration of response (DOR), progression-free survival (PFS), event-free survival (EFS), overall survival (OS), time to onset of CRS and NE, duration of CRS and NE, are provided below.

1) DOR

DOR analysis will only be performed for subjects with objective response.

Table 2. Analysis of DOR without Censoring by SCT for Subjects with Objective Response

Earliest Scenario since First Objective Response among PD, Death, New Therapy (excl. SCT), End of Study including W/D of Consent and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy (including retreatment but excluding SCT)	Censored	Last evaluable disease assessment date prior to the first new therapy (including retreatment), regardless of SCT
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Remain in response by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date

Abbreviations: DOR, duration of response; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First response date + 1.

Table 3. Sensitivity Analysis of DOR with Censoring by SCT for Subjects with Objective Response

Earliest Scenario since First Objective Response among PD, Death, New Therapy, SCT, End of Study including W/D of Consent and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy (including SCT and re-treatment)	Censored	Last evaluable disease assessment date prior to the first new therapy (including SCT and re-treatment)
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Remain in response by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date

Abbreviations: DOR, duration of response; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First response date + 1.

2) PFS

Table 4. Analysis of PFS without Censoring by SCT

Earliest Scenario since Infusion among PD, Death, New Therapy (excl. SCT), End of Study including W/D of Consent and Lost to Follow Up and No Post-infusion Disease Assessment	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy (including retreatment but excluding SCT)	Censored	Last evaluable disease assessment date prior to the first new therapy (including retreatment), regardless of SCT
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Progression-free and alive by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed	Censored	axicabtagene ciloleucel infusion date

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First infusion date + 1

Table 5. Sensitivity Analysis of PFS with Censoring by SCT

Earliest Scenario since Infusion among PD, Death, New Therapy, SCT, End of Study including W/D of Consent and Lost to Follow Up and No Post-infusion Disease Assessment	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy (including SCT and re-treatment)	Censored	Last evaluable disease assessment date prior to the first new therapy (including SCT and re-treatment)
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Progression-free and alive by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed	Censored	axicabtagene ciloleucel infusion date

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First infusion date + 1

3) EFS

Table 6. Analysis of EFS without Considering SCT as Event

Earliest Scenario since Infusion among PD, Death, New Therapy (excl. SCT), End of Study including W/D of Consent and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy (excluding SCT)	Event	Last evaluable disease assessment date prior to the first new therapy
Axicabtagene ciloleucel re-treatment	Event	Last evaluable disease assessment date prior to re-treatment
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Event-free by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed	Censored	axicabtagene ciloleucel infusion date

Abbreviations: EFS, event-free survival; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date – First infusion date + 1

Table 7. Sensitivity Analysis of EFS Considering SCT as Event

Earliest Scenario since Infusion among PD, Death, New Therapy, SCT, End of Study including W/D of Consent and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-lymphoma therapy	Event	Last evaluable disease assessment date prior to the first new therapy
SCT	Event	Last evaluable disease assessment date prior to first SCT
Axicabtagene ciloleucel re-treatment	Event	Last evaluable disease assessment date prior to re-treatment
End of study including withdrawal of consent and lost to follow-up	Censored	Last evaluable disease assessment date prior to EOS date
Event-free by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed	Censored	axicabtagene ciloleucel infusion date

Abbreviations: EFS, event-free survival; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First infusion date + 1

4) OS

Table 8. Analysis of OS

Circumstance	Event/Censored	Date of Event/Censoring
Death (non-missing death date ≤ cutoff date)	Event	Death date
Alive (either death date or last known alive date > cutoff date)	Censored	Data cutoff date
Alive (death date is missing and last known alive date ≤ cutoff date)*	Censored	Last known alive date

Abbreviation: OS, overall survival.
Note: Time to event = Event / Censoring date - First infusion date + 1
* If the subject withdrew full consent or was lost to follow up prior to data cutoff date, then such information will be indicated in the summaries of OS.

5) Time to onset of first CRS (or NE)

Table 9. Analysis of Time to Onset of First CRS (or NE)

Circumstance	Event/Censored	Date of Event/Censoring
CRS (or NE) event(s)	Event	Earliest CRS (or NE) start date
No CRS (or NE) event, and subject died on or before data cutoff date	Censored	Death date
No CRS (or NE) event, and subject ended study due to consent withdrawal	Censored	Date of end of study
No CRS (or NE) event, and subject is alive or died after cutoff date, or lost to follow-up	Censored	Last known alive date

Note: Time to event = Event / Censoring date - First infusion date + 1

6) Duration of CRS (or NE)

Table 10. Analysis of Duration of CRS (or NE)

Circumstance	Event/Censored	Date of Event/Censoring
CRS (or NE) event(s) resolved, i.e. end date not missing and end date does not equal to death date	Event	Latest CRS (or NE) end date
CRS (or NE) end date equals to death date	Censored	Death date
CRS (or NE) end date is missing and subject ended study due to consent withdrawal	Censored	Date of end of study
CRS (or NE) end date is missing, and subject is alive or died after cutoff date, or lost to follow-up	Censored	Last known alive date

Note: Duration = Event / Censoring date - earliest CRS/NE start date + 1

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Patient Safety eSigned	21-Nov-2023 20:15:39
PPD	Biostatistics eSigned	21-Nov-2023 21:00:23
PPD	Clinical Development eSigned	27-Nov-2023 19:54:25