Official Title of Study:

A Phase 2 Study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (TRANSCEND-PILOT-017006)

PROTOCOL: 17006

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STATISTICAL ANALYSIS PLAN

A Phase 2 Study of Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (017006)

STUDY DRUG:	JCAR017
PROTOCOL NUMBER (DATE):	Amendment 6 (16 August 2021)
ANALYSIS PLAN VERSION:	3.0
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Statistical Therapeutic Area Head

Signature [redacted] Date: 2021.08.02 17:17:38 -07'00'

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1. LIST OF ABBREVIATIONS

Table 1. Abbreviations and Specialist Terms

Abbreviation or Term	Definition/Explanation
aaIPI	age-adjusted international prognosis index
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL	acute lymphoblastic leukemia
Allo-HSCT	allogeneic hematopoietic stem cell transplant
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
ATA	anti-therapeutic antibody
AUC	area under the curve
CAR	chimeric antigen receptor
CBC	complete blood count
Cmax	maximum concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate

CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHL/THL	double hit lymphoma/triple hit lymphoma
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusions
DMSO	dimethyl sulfoxide
DOR	duration of response
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate

EGFRt	truncated human epidermal growth factor receptor
EOS	End-of-Study
FDA	Food and Drug Administration
flu/cy	fludarabine and cyclophosphamide
GCB	germinal center B-cell
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage colony-stimulating factor
GVHD	graft versus host disease
HCT-CI	hematopoietic cell transplant specific comorbidity index
HEOR	health economics and outcomes research
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IB	Investigator's brochure
IBC	Institutional Biosafety Committee
ICE	Immune Effector Cell-Associated Encephalopathy
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit

IFNγ	interferon gamma
IgA, G, or M	Immunoglobulin A, G, or M
iiNT	Investigator-identified neurological toxicity
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous
KM	Kaplan-Meier
LDC	lymphodepleting chemotherapy
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NOS	not otherwise specified

NT	neurologic toxicities
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCP	Pneumocystis pneumonia
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PO	per os (orally)
PRO	patient-reported outcome
qPCR	quantitative polymerase chain reaction
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
RCL	replication-competent lentivirus
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class

SPD	sum of the product of the perpendicular diameters
SPM	second primary malignancy
tDLBCL	transformed DLBCL from indolent histology
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TNE	transplant ineligible

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planed statistical analyses and data presentations for protocol 017006 Amendment 6 "A Phase 2 Study of lisocabtagene maraleucel (JCAR017) as Second-Line Therapy in Adult Patients with Aggressive B-cell NHL (017006)" which was issued on 16 August 2021. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one primary and one final analysis. The final analyses will be carried out after all subjects have completed or discontinued the study due to any reason. No formal hypothesis testing will be performed at the final analysis.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock for the primary/final analysis. This SAP will be finalized and signed prior to the clinical database lock for the primary analysis. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.4 or higher.

JCAR017 is defined as a product lot that met all manufacturing release specification limits at the time of release. Any product wherein one or both components (CD4+ and CD8+ CAR+ T cells) did not meet a release specification limit was considered nonconforming product. Throughout this document, "JCAR017" refers to conforming product unless specified otherwise.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to assess the antitumor activity of JCAR017 in adult subjects with aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for hematopoietic stem cell transplantation (HSCT).

3.2. Secondary Objectives

- To evaluate the safety of JCAR017
- To assess the rate of complete response (CR) and durability of anti-tumor activity of JCAR017
- To estimate the progression-free survival (PFS), event-free survival (EFS) and overall survival (OS) of subjects treated with JCAR017
- To characterize the pharmacokinetic (PK) profile of JCAR017 in this subject population
- To assess health-related quality of life (HRQoL) and health economics and outcomes research (HEOR)

3.3. Exploratory Objectives

- To assess immune responses to JCAR017
- To assess the pharmacodynamic effects of JCAR017
- To assess CAR T subset expansion and persistence
- To assess the effect of JCAR017 attributes on safety, PK, and antitumor activity
- To assess the effect of tumor and tumor microenvironment on JCAR017 PK and clinical response

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is an open-label, multicenter, Phase 2 study to determine the antitumor activity, PK, and safety of JCAR017 in subjects who have relapsed from, or are refractory to, frontline immunochemotherapy for aggressive B-cell NHL and are ineligible for transplant. Subjects will be treated with lymphodepleting chemotherapy and JCAR017.

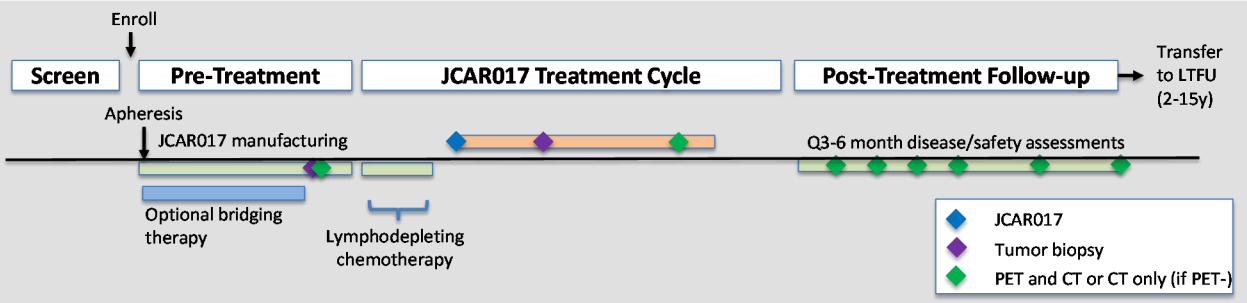
A schematic of treatment for each subject is provided in Figure 1. Upon enrollment, subjects will undergo leukapheresis to enable JCAR017 product generation. A baseline tumor biopsy (either an historical sample or, if not available, fresh tumor sample) for disease confirmation will be obtained. While JCAR017 is being manufactured, if required to control disease, subjects may receive salvage low-dose chemotherapy or one cycle of non-curative standard of care antitumor therapy.

Upon successful JCAR017 product generation, subjects will enter the treatment phase. Treatment includes lymphodepleting chemotherapy with fludarabine/cyclophosphamide (flu/cy) followed by JCAR017 administered IV 2 to 7 days after completion of lymphodepleting chemotherapy.

After administration of JCAR017, subjects will enter post-treatment follow-up, and will be followed on this study for 2 years for safety, PK and biomarkers, disease status, HRQoL, and survival. After completion of 2 years of assessments in this protocol, long-term follow-up (LTFU) for survival, long-term toxicity, and viral vector safety will continue under a separate protocol for up to 15 years.

Toxicity will be evaluated on an ongoing basis by the study team and reviewed at regularly scheduled Investigator Safety calls. Additionally, safety monitoring boundaries based on the incidence of Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity and prolonged Grade 4 and Grade 5 individual safety events will be established using a Bayesian framework (Thall 1994, Yao 2013). If the safety boundaries are crossed, enrollment will be paused and ad hoc Data Safety Monitoring Board (DSMB) meetings will be held to review the data. The study will remain paused for enrollment pending the DSMB recommendations.

Figure 1. Study Schema for Individual Subjects



4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint(s)

The primary (efficacy) endpoint is overall response rate (ORR [CR + partial response (PR)]).

4.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints are:

- CR rate, defined as the proportion of subjects with a best overall response (BOR) of CR
- Duration of response (DOR) and DOR for subjects whose best overall response is CR, each defined as the time from first response to progressive disease (PD) or death
- PFS, defined as the time from JCAR017 infusion to PD or death
- EFS, defined as time from JCAR017 infusion to the earliest of the following events: death from any cause, PD, or starting a new anticancer therapy.
- OS, defined as the time from JCAR017 infusion to death
- Numbers of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization
- Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the FACT-Lym subscale and the EuroQol instrument EQ-5D-5L

4.2.3. Safety and PK Endpoints

- Type, frequency, and severity of AEs and laboratory abnormalities
- Maximum concentration (C_{max}), time to peak concentration (T_{max}), area under the curve (AUC) and other relevant PK parameters of JCAR017 in blood as assessed by quantitative polymerase chain reaction (qPCR)

4.2.4. Exploratory Endpoint(s)

- Measurement of anti-therapeutic antibodies (ATA) to JCAR017
- Measurement of pharmacodynamic biomarkers in peripheral blood including CD19+ B cell numeration, serum immunoglobulin, soluble biomarkers (cytokines and chemokines), and inflammatory markers (CRP and ferritin)
- JCAR017 product characteristics (e.g. T-cell subsets, transduction efficiency, immunophenotype and gene expression at time of administration and post-dose)
- Measurement of CD4+ and CD8+ CAR T cell numbers per mL in blood by flow cytometry

- Evaluation of tumor biopsies for CD19 expression and attributes of tumor and tumor microenvironment, including, but not limited to, the presence of regulatory T cells and expression of immune checkpoint markers

4.3. Stratification, Randomization, and Blinding

Not Applicable.

4.4. Sample Size Determination

A sample size of approximately 62 subjects in the JCAR017-treated Efficacy Analysis Set for Study 017006 would provide at least 85% power to reject the null hypothesis of overall response rate ≤ 50% assuming the target overall response rate of 70% using an exact binomial test with 1-sided significance level 0.025. The null hypothesis of 50% ORR used to size the study is supported by the meta-analysis presented in Protocol Section 1.1. EAST v6.4.1 is used to calculate the sample size and power. Assuming a 15% drop-out rate from leukapheresis prior to JCAR017 infusion, it is anticipated that approximately 73 subjects will be leukapheresed in the study.

Table 2. Power calculation for rejecting the null hypothesis over a range of potential overall response rate estimates from the retrospective patient-level real-world cohort, assuming a target overall response rate of 70% using an exact binomial test with 1-sided significance level 0.025 and a sample size of 62 subjects

pa	p0	Power
70%	45%	96.9%
70%	47.5%	94.6%
70%	50%	86%
70%	52.5%	79.1%
70%	55%	60.5%

Abbreviations: pa, the overall response rate in JCAR017-treated Efficacy Analysis Set; p0, the overall response rate from retrospective patient-level real-world cohort.
EAST v6.4.1 is used to calculate the power.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- Data from all study centers will be combined for analysis
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous variables
- All mean, median, and quartile values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value
- All percentages will be rounded to one decimal place unless specified otherwise. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses
- All listings will be sorted for presentation in order of study center, subject, and date of procedure or event
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects in that analysis population)
- The day of the first dose of JCAR017 will be defined as Day 1
- Baseline value will be defined as the last value on or before the first dose of JCAR017 is administered; if multiple values are present for the same date, the average of these values (continuous variable) or the value with the lowest severity (categorical variable) will be used as the baseline. For subjects who were not treated, the baseline will be the latest non-missing value.
- Pre-Lymphodepleting chemotherapy (LDC) value will be defined as the latest measurement take on or prior to the start date of the last LDC prior to the JCAR017 infusion.
- The following rules will be used to assign one value to each post-baseline time point at the subject level:
  - If a value is available at a scheduled visit (e.g., Day 29), then that value will be used for the visit, regardless of whether a value is available from an unscheduled visit that is within the same analysis period.

- If the value at a scheduled visit is missing but a value is available at an unscheduled visit within the visit window, the value from the unscheduled visit closest to the nominal day will be used for the time point. If values from more than one unscheduled visit met the criteria, then the one with the later date will be used for the visit.
- If there are multiple values recorded on the same day, and a numeric value is used to derive a categorical variable, the value that corresponds to the most severe categorical derivation will be selected. Otherwise the average (arithmetic mean or geometric mean, as appropriate) will be used.
- If the value at a scheduled visit is missing and there is no value available from an unscheduled visit within the visit window, the value at the visit will be missing.

Table 3. Nominal visits and associated visit windows

Nominal Visit	Nominal Day	Lower Limit	Upper Limit
Screening	-9999	-9999	1st leukapheresis
Pretreatment	1st leukapheresis + 1	1st leukapheresis + 1	1st day of last LDC
Day 1	1	1st day of last LDC + 1	1
Day 4	4	2	5
Day 8	8	6	9
Day 11	11	10	12
Day 15	15	13	18
Day 22	22	19	25
Day 29	29	26	44
Day 60/Month 2	60	45	75
Day 90/Month 3	90	76	135
Day 180/Month 6	180	136	225
Day 270/Month 9	270	226	318
Day 365/Month 12	365	319	405
Day 455/Month 15	455	406	500
Day 545/Month 18	545	501	638
Day 730/Month 24	730	639	≥ 730

5.2. Analysis Populations

5.2.1. Screened Analysis Set

The Screened Analysis Set will include all subjects who have signed informed consent.

5.2.2. Eligible Analysis Set

The Eligible Analysis Set will include all subjects who have signed informed consent and who meet all inclusion/exclusion criteria.

5.2.3. Leukapheresed Analysis Set (i.e. Intent-to-treat Analysis Set)

The Leukapheresed Analysis Set will include all subjects who have signed informed consent, and who undergo leukapheresis.

5.2.4. JCAR017-treated Analysis Set

The JCAR017-treated Analysis Set will include all subjects who have received at least one infusion of JCAR017 cell product.

5.2.5. JCAR017-treated Efficacy Analysis Set

The JCAR017-treated Efficacy Analysis Set will include all subjects in the JCAR017-treated Analysis Set who have PET-positive disease present before JCAR017 administration based on independent review committee (IRC) assessment. Subjects who do not have baseline PET/CT assessment repeated after bridging therapy and before JCAR017 administration will be excluded from the JCAR017-treated Efficacy Analysis Set.

5.2.6. Pharmacokinetic Analysis Set

- qPCR Pharmacokinetic Analysis Set

The qPCR PK analysis set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on study PK measurements as assessed by qPCR.

- Flow Cytometry Pharmacokinetic Analysis Set

The flow cytometry PK analysis set includes subjects in the JCAR017-treated Analysis Set who have both baseline and on study PK measurements as assessed by flow cytometry.

5.2.7. Outpatient Analysis Set

The Outpatient Analysis Set includes all subjects in the JCAR017-treated Analysis Set who are monitored as outpatient following JCAR017 administration.

5.2.8. Patient-reported Outcome Analysis Set

- PRO/QoL QLQ-C30 Evaluable Set

  The PRO/QoL EORTC QLQ-C30 Evaluable Set includes subjects who have a baseline and at least one post baseline assessment that is analyzable in the JCAR017-treated Analysis Set. The EORTC QLQ-C30 is considered analyzable if at least one subscale is completed.

- PRO/QoL FACT-LymS Evaluable Set

  The PRO/QoL FACT-LymS Evaluable Set includes subjects whose baseline are analyzable and at least one post baseline scale is analyzable in the JCAR017-treated Analysis Set. Questionnaire is analyzable if more than 50% (i.e. a minimum of 8 of the 15 items) are answered.

- PRO/QoL EQ-5D-5L Evaluable Set

  The PRO/QoL EQ-5D-5L Evaluable Set includes subjects who have completed five-dimension measures at baseline and post baseline in the JCAR017-treated Analysis Set.

- PRO/QoL EQ-VAS Evaluable Set

  The PRO/QoL EQ-VAS Evaluable Set includes subjects who have completed visual analogue scale (VAS) at baseline and at post baseline in the JCAR017-treated Analysis Set.

6. SUBJECT DISPOSITION

Based on the Screened Analysis Set, the number and percentage of subjects who are in the Eligible Analysis Set, who undergo leukapheresis, who receive JCAR017 or nonconforming product will be summarized. The summary will also include the number and percentage of subjects who failed screening, the number and percentage of subjects who are in the Eligible Analysis Set but do not undergo leukapheresis, and who undergo leukapheresis but do not receive JCAR017 or nonconforming product, with reasons for not receiving product infusion.

There will also be a summary of subject disposition that presents the number and percentage of subjects in each of the categories listed below in the JCAR017-treated Analysis Set:

- Ongoing
- Completed study
- Discontinued the study with reasons for premature discontinuation
- Enrolled in the long-term follow-up study
- Subjects received retreatment

Note that reasons for discontinuing the study prematurely will be collected on the CRF and will be summarized with the following categories in the JCAR017-treated Analysis Set.

- Adverse event
- Withdrawal by subject
- Subject lost to follow-up
- Death
- Study terminated by sponsor
- Other

Reasons of discontinuation will be summarized in Leukapheresed Analysis Set.

Reasons of screen failure will be provided to support the above summary tables.

7. PROTOCOL DEVIATIONS/IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations were identified and assessed by clinical research physician or designee following company standard operational procedure. Important protocol deviations will be summarized for the JCAR017-treated Analysis Set.

A by-subject listing of subjects with protocol deviations/important protocol deviations in the Leukapheresed Analysis Set will be provided.

COVID-19-related protocol deviations will be also summarized and listed in a similar fashion as described above.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized for the Leukapheresed Set, and JCAR017-treated Analysis Set. Individual subject listings will be provided to support the summary tables.

8.1. Demographics and Baseline Characteristics

Age (years) at screening will be summarized descriptively. Age category (< 65, ≥ 65 to <70, ≥ 70 to < 75, ≥75), sex, race, and ethnicity will be summarized by frequency counts.

Age will be calculated as follows: age = Integer ≤ [(Date of screening – Date of Birth + 1) / 365.25].

The following will also be summarized based on the latest weight and height prior to JCAR017:

- Height (cm)
- Weight (kg)
- BMI (weight (kg)/ height (m^2))

Age-adjusted International Prognosis Index (aaIPI), electrocardiogram (ECG) status, hematopoietic cell transplant specific comorbidity index (HCT-CI) score, and TNE criteria met will be summarized.

8.2. Disease Characteristics

The following disease characteristics will be summarized:

- Type of B-NHL (DLBCL NOS, transformed follicular lymphoma [tFL], high grade lymphoma with DLBCL histology, follicular lymphoma Grade 3B)
- Cell of origin (GCB, ABC/non-GCB, Unknown)
- Time (months) since initial B-NHL diagnosis to JCAR017 infusion

  For partial diagnosis date, if the day and month are missing but the year is available, then the imputed day and month will be 01 Jul or the first prior NHL treatment date if they have the same year, whichever is earlier. If the day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Sum of the product of the perpendicular diameters (SPD) per IRC at pre-LDC
- Lactate dehydrogenase (LDH) at pre-LDC
- C-reactive protein (CRP) at baseline (pre-JCAR017 infusion)
- CNS involvement
- Eastern Cooperative Oncology Group (ECOG) performance status at screening, pre-LDC, and pre-JCAR017 infusion
- Best response to prior therapies after diagnosis

- Prior response status:
    - Refractory versus relapsed. The status is refractory if a subject achieved less than a CR to front line therapy; otherwise the status is relapsed.
    - Refractory or relapsed disease ≤ 12 months (defined as CR lasting no more than 12 months) versus relapsed later than 12 months, to front line therapy.
    - Refractory (BOR to front line therapy of PD/SD/PR) or CR lasting < 3 months versus CR lasting ≥ 3 months and ≤ 12 months.
    - Chemorefractory (BOR to front line therapy of PD/SD) versus chemosensitive (BOR of CR/PR)
- Time from last systemic regimen to JCAR017 infusion (in months)
- International prognostic index at screening
- Ann Arbor stage at screening
- Bone marrow involvement at baseline (pre-JCAR017 infusion)

8.3. Medical History

A by-subject listing of medical history will be presented.

8.4. Prior Therapy

Prior NHL therapies include all therapies received after NHL diagnosis date and prior to the first JCAR017 infusion, excluding anticancer treatment for disease control. Type of prior therapy will be summarized using descriptive statistics. The following will be summarized for prior treatment:

- Type of last line of therapy prior to JCAR017
- Time (months) from last systemic regimen to JCAR017

  For partial prior therapy start date, if the day and month are missing but the year is available, then the imputed day and month will be 01 Jan if it has a different year than the diagnosis date, or the diagnosis date if they have the same year. If the day is missing but the month and year are available, then the imputed day will be the first day of the month if start date of prior therapy and date of diagnosis have a different year or different month, or the prior therapy start date will be imputed by date of diagnosis if they have the same year and month.

8.5. Prior and Concomitant Medications

8.5.1. Anticancer Treatment for Disease Control

Anticancer treatment for disease control is defined as any chemotherapy provided to subjects in the time period after signing consent and prior to lymphodepletion. Number and percentage of subjects receiving therapy, as well as type of therapy (platinum-based vs. non platinum based) will be summarized. Number and percentage of subjects with CR after receiving anticancer treatment for disease control will also be reported.

8.5.2. Prior Medications

Prior medications are defined as medications that were ended before the start of JCAR017. A summary showing the number and percentage of subjects who took prior medications will be presented by WHO therapeutic drug class (ATC level 1) and preferred term.

8.5.3. Concomitant Medications

Concomitant medications are defined as medications that were either initiated before and continued after the first dose of JCAR017, or initiated on/after the date of the first dose of JCAR017.

A summary showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class (ATC level 1) and preferred term.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Exposure to the study treatment will be summarized based on JCAR017-treated Analysis Set. A by-subject listing will also be presented.

9.1. Lymphodepleting Chemotherapy

Details of exposure to LDC – fludarabine and cyclophosphamide will be presented for JCAR017-treated Analysis Sets.

Number and percentage of subjects will be presented for whether the dose was administered, reasons if not administered, whether the dose was reduced along with the reason for dose reduction.

Time from last dose date of lymphodepleting chemotherapy to first dose date of JCAR017 will be summarized by descriptive statistics.

9.2. JCAR017 Infusion

JCAR017 is defined as a product lot that met all manufacturing release specification limits at the time of release. Any product wherein one or both components did not meet a release specification limit was considered nonconforming product. Throughout this document, "JCAR017" refers to conforming product unless specified otherwise.

Details of exposure to JCAR017 will be summarized on JCAR017-treated Analysis Set. The CD4, CD8 and JCAR017 dose (volume and number of cells) administered to subjects will be summarized.

Number and percentage of subjects who received JCAR017 retreatment will be summarized.

Total on-study follow-up time will be summarized using descriptive statistics.

The on-study follow-up time is defined as the end-of-study (EOS) date minus first dose date plus 1, and will be expressed in months. If subjects are continuing on study, the earliest of the last known alive date or the data cutoff date will be used to impute the EOS date for the purpose of the calculation. The number and percentage of subjects followed for at least 1 day, 29 days, as well as 2, 3, 6, 9, 12, 18, and 24 months will be summarized. Total follow-up time will be provided.in person-years.

10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the JCAR017-treated Efficacy Analysis Set. Two-sided confidence intervals (CIs) for intended point estimates will be reported. Efficacy evaluations will be conducted using the Leukapheresed Analysis Set as sensitivity analysis.

Efficacy endpoints may be analyzed separately for subjects who received nonconforming product.

10.1. Multiplicity

The primary hypothesis shown below will be tested on the 017006 data at the time of the primary analysis. Administrative efficacy analyses may be performed per health authorities' requests without any intention for hypothesis testing or change of study conduct, therefore, no adjustment for multiplicity is needed.

10.2. Analysis of Primary Efficacy Endpoint

The primary endpoint of the study is the independent review committee (IRC)-reviewed ORR, defined as the proportion of subjects with a best overall response (BOR) of either CR or PR based on the Lugano 2014 criteria. The BOR is the best disease response recorded from the time of the JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy or JCAR017 retreatment. Best response will be assigned according to the following order: CR, PR, SD, PD, not evaluable, or not done. The null hypothesis used for estimating study sample size was derived from a meta-analysis of 2L DLBCL studies with similar but not identical populations compared to the population to be enrolled in the current study. A retrospective patient-level real-world data cohort will be used as a more comparable external/synthetic control to provide the reference rate for the null hypothesis for testing the primary endpoint of ORR. Generation of the external control will be described in a real-world evidence (RWE) Study CA082-014 SAP.

The primary efficacy analysis will test the null hypothesis of ORR $\leq$ p0% against the alternative hypothesis that the ORR > p0% using exact Binomial test with a 1-sided 0.025 level of significance based on the JCAR017-treaed Efficacy Analysis Set.

Considerations for the primary estimand and the supplementary estimand can be found in Appendix 16.4.

10.2.1. Timing of Analyses

The primary analysis is planned after approximately 62 subjects have been treated with JCAR017, and these subjects have been followed for at least 6 months after first response (either CR or PR), or until death, progressive disease, or withdrawal from study.

Hypothesis testing will only be performed at the time of the primary analysis.

The final analyses will be carried out after all subjects have completed or discontinued the study due to any reason. No formal hypothesis testing will be performed at the final analysis.

10.3. Analyses of Secondary Efficacy Endpoints

10.3.1. CR Rate

The CR rate, defined as the proportion of subjects with a best overall response of CR based on the IRC assessment.

10.3.2. DOR and DOR for Subjects Whose BOR is CR

Duration of response (DOR) and DOR for subjects whose best overall response BOR is CR, each defined as the time from first documentation of CR or PR to progressive disease (PD) or death. The first documentation of CR or PR is defined as the latest of all dates of required measurements to establish the response. The progression date is defined as the earliest date of all assessments that lead to a progression.

DOR will be evaluated based on the IRC evaluations for subjects who achieve a response (CR or PR) using the Lugano 2014 criteria and study-specific criteria specified in the Bioclinica Charter. The date of first response and the date of progression will be assigned by the IRC. A response is considered adequate if the assessment was performed and the outcome of assessment was other than "not evaluable" or "not done." In addition, DOR will be evaluated for subjects who achieve a CR.

If a subject does not have an event for the DOR analysis, the subject will be censored based on censoring rules in Table 4 below.

Kaplan-Meier (KM) methodology will be used to analyze DOR and DOR for subjects whose BOR is CR, KM estimates of DOR at 6, 12, 18, and 24 months post initial response will be provided.

DOR analysis will also be performed for subjects whose BOR is PR.

10.3.3. PFS and OS

PFS is defined as the time from JCAR017 infusion to PD or death.

OS is defined as the time from JCAR017 infusion to the date of death.

If a subject does not have an event for the PFS analysis, the subject will be censored based on censoring rules in Table 4 below.

For assessment of OS, data from surviving subjects will be censored at the last time that the subject is known to be alive. The OS analysis will include all available survival information from the long-term follow-up study (GC-LTFU-001) if applicable.

Analysis of PFS and OS will be stratified by responses: CR, PR, and non-responders.

KM methodology will be used to estimate the rate of PFS or OS at months 6, 12, 18, and 24, and the median PFS or OS along with the 95% CI. PFS analysis will be conducted using both FDA and EMA censoring rules as sensitivity analyses.

Table 4. Event and Censoring Rules for DOR and PFS

Scenario	FDA Censoring Rule		EMA Censoring Rule	
	Censor/Event	Date	Censor/Event	Date
Death or Documented PD	Event	Documented PD or Death date whichever is earlier	Event	Documented PD or Death date whichever is earlier
Start new anti-lymphoma therapy before PD/Death [a]	Censor	Last adequate assessment date with no evidence of PD before starting new subsequent anti-lymphoma therapy	Event	Documented PD or Death date whichever is earlier
No documented PD and no Death	Censor	Last adequate assessment date with evidence of no PD	Censor	Last adequate assessment date with evidence of no PD

Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration
[a] Conditioning therapy of HSCT and start of JCAR017 retreatment are considered as the start of new anti-lymphoma therapy.

10.3.4. Event-free survival

Event-free survival is defined as the interval from the date of JCAR017 infusion to the earliest of the following events: death from any cause, progressive disease, or starting a new anticancer therapy or JCAR017 retreatment.

The censoring rules for EFS are shown in Table 5 below.

The KM method will be used to estimate the rate of EFS at months 6, 12, 18, and 24, and the median EFS along with the 95% CI.

Table 5. Censoring Rules for EFS

Scenario	FDA and EMA Censoring Rule

	Censor/Event	**Date**
Death or Documented PD without new anticancer therapy	Event	Documented PD or Death date whichever is earlier
Start new anti-lymphoma therapy before PD/Death [a]	Event	Date of new anti-lymphoma therapy
No documented PD and No Death and No new anti-lymphoma therapy	Censor	Last adequate assessment date with evidence of no progression or anti-lymphoma therapy

Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration.
[a] Conditioning therapy of HSCT and start of JCAR017 retreatment are considered as the start of new anti-lymphoma therapy.

10.3.5. Pharmacokinetic Analyses

Assessment of JCAR017 PK will be determined by quantitative PCR (qPCR) to detect the JCAR017 transgene. Flow cytometry analysis will be performed as an exploratory endpoint to enumerate the number of JCAR017 cells (CD3+, CD3+CD4+ and CD3+CD8+ CAR T cells).

For both qPCR-based and flow cytometry-based PK assays, the following PK parameters will be derived for JCAR017 by noncompartmental analysis as appropriate:

- Maximum concentration (C_{max});
- Time to maximum concentration (T_{max});
- Area under the curve from JCAR017 infusion through 28 days after infusion (ie, from Day 1 to Day 29; AUC_{0-28});

Actual sampling days will be used in the calculations of PK parameters. Additional PK parameters may be determined when appropriate.

For both qPCR-based and flow cytometry-based PK assays, blood concentrations and PK parameters will be listed and summarized by nominal time/visit using descriptive statistics (N, mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, median, Q1, Q3, minimum, and maximum). Individual and median (Q1, Q3) concentration versus time profiles will be generated. Relationships between PK parameters and select efficacy or safety endpoints may be explored using descriptive statistics and/or statistical tests as deemed appropriate. Relationships between PK parameters and demographics and disease characteristics may also be explored.

For noncompartmental analysis, qPCR-based concentrations that are below the lower limit of quantification (LLOQ) will be assigned a numerical value of 0. Flow cytometry-based

concentrations that are below the lower limit of the detection (LLOD) will be assigned a numerical value of 0.

For the calculation of descriptive statistics and plotting, qPCR-based concentration below the LLOD will be imputed to (minimum value)/2 for analysis. No data imputation will be conducted for values below the LLOQ but above the LLOD. Any numerical values obtained before the JCAR017 infusion will be included in the analysis as 0. Flow cytometry-based concentration below the LLOD will be imputed to LLOD/2. Any numerical values obtained before the JCAR017 infusion will be included in the analysis as 0. Negative values can occur due to background subtraction and all negative values will be set to 0.

Persistence of JCAR017 in blood will be assessed based on both qPCR and flow cytometry assays. Persistence of JCAR017 at a time point as assessed by qPCR is defined as a transgene count greater than or equal to the LLOD. Persistence of CD3+ CAR T cells is defined as a CD3+ CAR T count greater than or equal to the LLOD of 0.1 cells/μL with at least 25 events captured in the CAR T flow cytometry detection gate. Persistence of CD4+ and CD8+ CAR T cells at a time point will be similarly defined. For both assays, data obtained after the start of a new anticancer therapy will not be included in the determination of persistence. Persistence will be summarized by scheduled visit.

10.3.5.1 Persistent Vector Sequencing (PVS) Monitoring

Persistent presence of CAR vector sequence, as assessed by qPCR, will be monitored in peripheral blood. Results will be summarized by scheduled visits for subjects receiving JCAR017 treatment and a listing of any subjects with PVS detected will be provided.

Persistent presence of vector sequence is defined as detection of transgene sequences in more than 1% of cells in blood collected at 12 months or any time after 12 months post-infusion of JCAR017.

10.4. Sensitivity Analysis

Sensitivity analyses of primary and secondary efficacy endpoints, including ORR, CR rate, DOR, PFS, and OS, will be performed based on:

- the Leukapheresed Set
- the response determined by investigator

The analysis method will be the same as described in Sections 10.2 and 10.3 for corresponding endpoints.

For efficacy analysis (ORR, CRR, PFS, EFS) based on the Leukapheresed Set, subjects who discontinued without receiving JCAR017 (or non-conforming product) will be counted as non-responders in the ORR/CRR analysis and will be censored at the date of first leukapheresis in the PFS/EFS analysis unless the patient died before infusion (event), given adequate response assessments are not collected in the clinical database for these subjects.

In addition, sensitivity analyses will be performed for efficacy endpoints based on IRC assessments, categorizing the below 4 scenarios as PD regardless of PET-based metabolic response at that time point.

- Complete metabolic response/partial metabolic response (CMR/PMR) on PET and disease progression on CT scan
- Stable metabolic disease (NMR) on PET and disease progression on CT scan
- New lesion on CT scan regardless of whether the new lesion is fluorodeoxyglucose (FDG) avid on PET
- Clinical (non-radiographic) PD per investigator, including exam findings

10.5. Subgroup Analysis

Efficacy subgroup analysis for ORR, CR, DOR, PFS, EFS and OS will be performed on the following variables:

1. Age: < 65 vs ≥ 65; < 70 vs ≥ 70, < 75 vs ≥ 75 at screening
2. Sex: male versus female
3. Ethnicity: Hispanic or Latino versus not Hispanic or Latino
4. Race: white versus other races
5. Prior response status:
    a. Refractory versus relapsed. The status is refractory if a subject achieved less than a CR to front line therapy; otherwise the status is relapsed.
    b. Refractory or relapsed disease ≤ 12 months (defined as CR lasting no more than 12 months) versus relapsed later than 12 months, to front line therapy
    c. Refractory (BOR to front line therapy of PD/SD/PR) or CR lasting < 3 months versus CR lasting ≥ 3 months and ≤ 12 months.
    d. Chemorefractory (BOR to front line therapy of PD/SD) versus chemosensitive (BOR of CR/PR)
6. CNS disease status: known CNS disease vs no known CNS disease at the time of the first JCAR017 infusion
7. SPD per IRC at pre-LDC: < 50 cm^2 vs ≥ 50 cm^2
8. LDH at pre-LDC: < 500 U/L vs ≥ 500 U/L
9. Screening HCT-CI: ≥ 3 versus <3
10. aaIPI score: $>=2$ vs ≤ 1
11. ECOG at screening: 0-1 vs 2
12. Anticancer therapy for disease control:
    a. Yes vs No
    b. platinum-based regimen, non-platinum based regimen, versus no bridging regimen
13. NHL subtype: DLBCL NOS, HGL, tFL, FL3B

14. Subgroups defined by age/organ function and disease status as shown in the table below:

	Response to 1L therapy of PD/SD/PR or CR lasting ≤ 12 months		
Meets all of the following criteria at screening: • Age ≤ 75 • ECOG 0-1 • ANC ≥ 1000/ul and platelets ≥ 50,000/ul • ALT ≤ 5 x ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL if Gilbert's syndrome or lymphomatous infiltration of the liver) • O_2 saturation ≥ 92% and Grade ≤ 1 dyspnea • LVEF ≥ 40% • CrCL > 45 ml/min (or Creatinine < 1.5 x ULN)		Yes	No
	Yes	A	B
	No	C	D

a. Subgroup A versus Subgroup B+C+D

b. Subgroup A+B versus Subgroup C+D

Subgroup analyses will be performed for the primary and secondary efficacy endpoints, if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups. Other subgroup analyses will also be performed if deemed appropriate.

10.6. Analyses of Exploratory Endpoints

10.6.1. Immunogenicity Analyses

Humoral immunogenicity assessment will include prevalence of immunogenicity (subjects with pre-existing antibodies that bind to JCAR017), incidence of immunogenicity (subjects with treatment-induced or treatment-boosted antibodies that bind to JCAR017), together with antibody titers. Data may be further fractionated to determine the proportion of subjects who make transient versus sustained antibody responses. The assay for humoral immunogenicity will be an enzyme-linked immunosorbent assay, detecting antibodies that bind to any potential epitope on the extracellular domain of the JCAR017 protein.

T cell-mediated responses to JCAR017 may also be evaluated by stimulating PBMCs with overlapping peptides from JCAR017 and measuring the cytotoxic T lymphocyte response using an enzyme-linked immunosorbent spot assay.

Humoral immunogenicity assessment and T cell-mediated responses to JCAR017 will be summarized at each visit on JCAR017-treated set.

Relationship between immunogenicity endpoints and select efficacy, safety, and PK endpoints may be explored using descriptive statistics and/or statistical tests as deemed appropriate.

10.6.2. Pharmacodynamic (PD) Biomarker Assessment

The biomarker assessments for JCAR017 will focus on evaluating:

Pharmacodynamic biomarker effects of JCAR017 by assessment of B-cell aplasia, serum immunoglobulins, soluble biomarkers and inflammatory markers (CRP and ferritin).

Pharmacodynamic Assessments

- B-cell Aplasia

  The incidence of B cell aplasia (defined as < 3% of CD19+ B cells in peripheral blood lymphocytes (Mueller, 2018) will be summarized by time point for scheduled visits.

- Serum Immunoglobulins

  Concentrations of Serum immunoglobulin IgA, IgG, and IgM will be summarized by time point for scheduled visits. In addition, the percentage of subjects with serum IgG concentrations < 500 mg/dL will be summarized by time point.

- Soluble Biomarkers

  Soluble biomarkers will be summarized by scheduled visits for actual values as well as fold-change values. Fold change will be defined as post-baseline divided by baseline. In addition, the Cmax, Tmax and the fold change for Cmax will be summarized.

- C-reactive protein (CRP) and ferritin

  C-reactive protein and ferritin will be analyzed in a manner analogous to that described for soluble biomarkers.

Relationship between pharmacodynamic endpoints and selected safety endpoints may be explored using descriptive statistics and/or statistical tests as deemed appropriate.

10.6.3. Replication-Competent Lentivirus (RCL) Testing

The presence of lentiviral vector sequences in blood, as measured using an analytically qualified qPCR method, will be summarized by scheduled visits and a listing of subjects with RCL detected will be provided.

10.6.4. Secondary Malignancy

In the event that secondary malignancy (also called second primary malignancy (SPM)) occurs, a sample of neoplastic tissue biopsy and blood will be requested for causality analysis. Tissue will be assessed for presence of transgenes by RNA-scope in-situ hybridization (ISH). Blood sample will be evaluated for RCL and tested for transgene by qPCR which is the same assay used for PK and PVS monitoring.

If transgene is detected in neoplastic tissue by ISH and/or more than 1% of cells in blood by qPCR, aliquots of the neoplastic tissue and/or blood will be submitted for insertion site analysis (ISA) to determine the locations of vector insertion sites and the frequency of insertion events to ascertain clonality. If a predominate insertion site is identified, further insertion site analysis will be conducted to assess the integration site in proximity to annotated cancer associated genes.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the JCAR017-treated Analysis Set. Subjects receiving nonconforming product will be summarized separately.

11.1. Adverse Events

Adverse events will be analyzed with a focus on treatment-emergent adverse events (TEAEs). TEAE is defined as any AE that starts from the date of JCAR017 infusion through and including 90 days after. Any AE occurring after the initiation of another anticancer treatment or JCAR017 retreatment will not be considered a TEAE.

If the onset date of an AE is incomplete, the imputed onset date (see Appendix 16.2.1 for imputation of partial AE dates) will be used to determine whether the AE is treatment-emergent, as long as the AE stop date is not prior to the JCAR017 infusion date.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first JCAR017 infusion date, will be considered to be treatment-emergent.

The incomplete dates will be shown in by-subject AE listings. The imputed dates will be used to define TEAE and used in time-to-event analyses or event onset or duration calculation.

All AEs will be coded using the Medical Dictionary for Regulatory Affairs® (MedDRA) dictionary.

A treatment-related AE is defined as an AE that was related to JCAR017 or lymphodepleting chemotherapy. AE relatedness to JCAR017 or lymphodepleting chemotherapy regimen (LDC) will always default to the investigator's assessment. Events starting on or after JCAR017 infusion or LDC, but for which the investigator does not record relationships to JCAR017 or LDC will be considered related to JCAR017 or LDC respectively for summary purposes. However, by-subject data listings will show the relationship as missing.

The intensity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 or higher by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5). A protocol-specified grading scale will be used to assess cytokine release syndrome (CRS) (Lee, 2014). If a subject experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same preferred term (system organ class), then the subject will be counted only once for that preferred term (system organ class). In addition, AEs with a missing intensity will be presented as an intensity category of "Missing" in summary tables and data listings.

The subject incidence of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs
- Grade 3 or higher TEAEs

- JCAR017-related TEAEs
- LDC-related TEAEs
- JCAR017-related Grade 3 or higher TEAEs
- Serious TEAEs
- JCAR017-related serious TEAEs
- TEAEs that led to death
- JCAR017-related TEAEs that led to death
- Most frequent TEAEs (≥ 5% by PT)
- All AEs reported after post treatment-emergent period (post treatment-emergent period starts from 91 days post JCAR017 administration, initiation of subsequent anticancer therapy, or JCAR017 retreatment started prior to day 91, whichever comes first), including LTFU data if applicable

In addition, all deaths will be summarized by period (≤ 30 days of first JCAR017 infusion, 31 - ≤ 90 days of JCAR, > 90 days of JCAR including LTFU data if applicable), with cause of death during each period.

AEs occurring after the JCAR017 retreatment will be summarized separately. Unless stated otherwise, the number of subjects who receive retreatment will be used as the denominator.

Data listing will be provided for the following:

- All AEs (with a variable indicating whether the event is treatment-emergent)
- SAEs
- AEs leading to death

COVID-19 AEs, identified by the COVID-19 standard MedDRA query (SMQ) with subsequent medical review for internal adjudication, will be summarized by preferred term and toxicity grade. A listing of COVID-19 AEs will be provided.

11.2. Adverse Events of Special Interest

A list of preferred terms to be included as AESIs is as follows:

Adverse events of special interest (AESI) for JCAR017 include the following TEAEs:

- **Cytokine Release Syndrome (CRS)**, based on the MedDRA PT "Cytokine release syndrome".
- **Investigator-identified neurological toxicity (iiNT),** based on the question "If related to liso-cel, is this a neurotoxicity event?" on the Adverse Event CRF
- **Infusion related reaction (IRR)**, using the MedDRA PT "Infusion related reaction" that is reported as related to JCAR017

- **Macrophage activation syndrome (MAS)**, using the MedDRA PT "Haemophagocytic lymphohistiocytosis"
- **Tumor lysis syndrome (TLS)**, using the MedDRA PT "Tumor lysis syndrome"
- **Serious infections**, based on Grade 3 or higher TEAE in infections and infestations SOC. Infections will be categorized by MedDRA high-level group terms (HLGT) as viral, bacterial, fungal or pathogen unspecified.
- **Prolonged cytopenias**, defined as Grade 3 or higher laboratory results of decreased haemoglobin, decreased neutrophil count, or decreased platelet count at the Study Day 29 visit (±2 days). Laboratory results occurring after the initiation of subsequent anticancer therapy or JCAR017 retreatment will not be considered. Recovery of prolonged cytopenias will be summarized for those subjects with hematology laboratory data after the Day 29 visit.

In addition, the following events can occur within or beyond the treatment-emergent period:

- **Hypogammaglobulinaemia**, which includes AEs that occurred on or after the first JCAR017 infusion date and coded to the following MedDRA PTs: of blood immunoglobulin A decreased, blood immunoglobulin D decreased, blood immunoglobulin E decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, immunoglobulins decreased, selective IgA immunodeficiency, selective IgG subclass deficiency and selective IgM immunodeficiency.
- **Second primary malignancy** (also referred as second malignancy) based on findings from SMQ searches for "Premalignant disorders" and "Malignancies" and subsequent medical review by an internal adjudication panel. This process consisted of review of preferred terms detected during SMQ search of all reported AE, and selecting those deemed appropriate for inclusion as malignancies.
- **Autoimmune disorders** based on finding from the search for the "Autoimmune disorders" HLGT plus the following additional PTs: temporal arteritis, granulomatosis with polyangiitis, vasculitis, Behcet's syndrome, and erythema nodosum, and subsequent medical review for internal adjudication.

The list and search terms for AESI may be updated prior to reporting. The AESI will be summarized by group term and search terms. If a subject experiences multiple events (with the same preferred term or different preferred terms) in an AESI category, the maximum grade across these events will be used as the maximum grade for that category.

In addition, duration of CRS and neurological toxicity, CRS and neurological toxicity by Grade, progression of Grade 1-2 to Grade 3 or higher will be summarized. The incidence of renal failure (dialysis), intubation, incidence of fever, incidence of hypotension, use of vasopressors will also be summarized.

Number of subjects who received tocilizumab to treat CRS and number of subjects who received corticosteroids to treat neurological toxicity will be summarized.

Time to onset and time to resolution of the first event of selected AESI will be summarized by descriptive summary statistics and KM estimates (as needed). Time to onset of the first event is defined as the time from Day 1, i.e., time in days is calculated as (start date of first occurrence of the event) – Day 1 +1. Multiple events in an AESI category occurring close to each other (e.g., if the start date of one CRS event is within 7 days of the end date of an earlier CRS event) will be considered as a single episode of event. Time to resolution of the first event is defined as the time from the start date of the first event to the end date of the last event in the episode. Subjects with any unresolved event in the episode are excluded from the time to resolution descriptive statistics summary. For KM analyses, in the absence of an event, subjects will be censored at the earliest of the following dates: date of EOS date, date of death, or date last known alive on study.

Descriptive statistics on Mini Mental State Examination (MMSE) baseline score, post-baseline score and change from baseline will be provided.

11.3. Clinical Laboratory Evaluations

A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade after the JCAR017 infusion and up to 90 days after the infusion prior to start of subsequent chemotherapy. The baseline value is defined as the last available recorded value on or prior to the date of the JCAR017 infusion. If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥1 in severity) will be considered treatment-emergent.

Applicable hematological and serum biochemistry laboratory data will be graded according to NCI CTCAE version 4.03 or higher. Grade 0 includes all non-missing values that do not meet criteria for an abnormality of at least Grade 1. The worst grade during the treatment-emergent period will be summarized. Frequency distributions for shift from baseline to the worst grade will be presented. Normal ranges will be used to determine the categories of High, Low, and Normal for lab tests that have no severity grade.

Furthermore, analyses may be repeated for selected laboratory parameters (e.g., cytopenia) by using the last observation collected prior to or on the date of initiation of the lymphodepleting chemotherapy regimen as baseline.

Listings of select clinical laboratory data will be provided by subjects and tests.

A list of clinical laboratory analytes to be summarized can be found in Appendix 16.3.

Data from each site's main laboratory will be used for analysis.

11.3.1. Hematology

In order to investigate the maximal degree of myelosuppression, the NCI CTCAE grade for absolute neutrophil counts (ANC), white blood cell counts (WBC), platelet counts, and hemoglobin will be summarized by the worst grade during the treatment-emergent period. The number and percentage of subjects with each NCI CTCAE grade will be presented. A shift table representing the shift from the baseline grade to the worst grade will be provided for ANC, WBC counts, platelet counts, and hemoglobin.

Cytopenia recovery, i.e., grade 3 or higher hemoglobin, neutrophils, or platelets at study day 29 visit and resolved to grade 2 or lower by study day 90, will be summarized.

11.3.2. Clinical Chemistry

Hepatic and renal function will be summarized using the NCI CTCAE grade for alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, and creatinine. The number and percentage of subjects that have each NCI CTCAE grade will be summarized using the worst grade during the treatment-emergent period. A shift table representing the shift from the baseline grade to the worst grade will be provided for each of these laboratory tests.

11.3.3. Other Labs

In addition to Hematology and Chemistry, data from the following labs will also be summarized: 1) Immunoglobulins (Immunoglobulins G, M and A), 2) Coagulation, 3) Inflammatory Markers.

11.4. Vital Sign Measurements

For vital signs at each visit and change from baseline at each visit will be summarized using descriptive statistics.

11.5. Electrocardiograms

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' at each visit. The shift from baseline to worst during the treatment-emergent period in the overall ECG interpretation will be summarized.

11.6. Safety Subgroup Analysis

In the JCAR017-treated Analysis Set, safety subgroup analyses will be performed on the same variables as specified in section 10.5. Subgroup analyses will be performed for key safety summaries, and will only be performed if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups. Other subgroup analyses will also be performed if deemed appropriate.

11.7 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will monitor this study (and other studies). The detailed roles and responsibilities of the DSMB and the scope of analysis to be provided to the DSMB are provided in a mutually agreed upon charter, which defines the DSMB membership, meeting logistics, and meeting frequency.

The DSMB will review cumulative study data approximately semi-annually over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial and

as needed to address any safety issues that may arise. The DSMB will provide advice to the Sponsor as outlined in the DSMB charter.

11.7.1 Safety Stopping Rules for Individual Events

Unexpected serious adverse events (SAEs) that are related to JCAR017 will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the DSMB, the Sponsor, and the Medical Monitor.

Study enrollment will be paused pending notification of the DSMB and appropriate regulatory authorities if any subject experiences any of the following events within 30 days of a JCAR017 cell product infusion:

- Life-threatening (Grade 4) toxicity attributable to JCAR017 that is unexpected, unmanageable (i.e., does not resolve to Grade 3 or lower within 7 days), and unrelated to chemotherapy.
- Death related to JCAR017.

The study will be terminated for the following reasons:

- Any subject develops uncontrolled JCAR017 proliferation that is unresponsive to treatment.
- Any subject develops detectable replication-competent lentiviruses (RCL) during the study
- The Sponsor, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or DSMB decides that subject safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of JCAR017 in this indication or the development of JCAR017 for all indications.

11.7.2 Safety Monitoring Boundaries

Besides the safety stopping rules for any individual safety event specified in Section 11.8.1, safety monitoring boundaries based on Bayesian framework (Thall 1994, Yao 2013) are included to help detect safety signals that may occur in the JCAR017-treated Analysis Set during the study. These boundaries are non-binding and the following toxicity events occurring within 30 days after JCAR017 cell product infusion will be considered as safety events of interest for monitoring:

- A Grade 3 or higher, JCAR017-related, treatment-emergent, investigator-identified neurological toxicity
- Grade 4 toxicity attributable to JCAR017 that is unexpected, unmanageable (ie, does not resolve to Grade 3 or lower within 7 days) and unrelated to chemotherapy.
- Grade 5 adverse events related to JCAR017

Based on the data from DF and DE stages of study 017001, we assume a prior distribution for the probability of the occurrence of toxicity events, $\pi_1 \sim$ Beta (0.15,0.85). If *n* out of *m* subjects experienced toxicity events listed above, then the posterior distribution of π_1 is Beta(0.15+*n*,0.85+(*m*-*n*)). Based on data reported in another CAR T Phase 2 trial (ZUMA-1) in a similar population with a sample size of 101, the Grade ≥ 3 neurological toxicity occurred in 28% of the patients (Neelapu 2017). Based on this data, a criterion function is defined as $Pr(\pi_1 > 40\% \mid data) > 0.9$. This criterion implies that the study will be paused when there is greater than 90% probability that the JCAR017-Treated Analysis Set experience a toxicity rate over 40%, and 40% represents ~43% relative increase in risk over the data reported in ZUMA-1 trial. The safety monitoring boundary values are shown in Table 6.

Whenever the safety boundaries are crossed, enrollment will be paused and ad hoc DSMB meetings will be held to review the data. The study will remain paused for enrollment pending the DSMB's recommendations.

Table 6. Safety Monitoring Boundaries Based on Thall and Simon (Thall 1994)

Number of Subjects Treated	Incidence
1-5	No Stopping
6-7	≥5
8-9	≥6
10-11	≥7
12-13	≥8
14-15	≥9
16-17	≥10
18-19	≥11
20-21	≥12
22-23	≥13
24-26	≥14
27-28	≥15
29-30	≥16
31-32	≥17
33-34	≥18
35-37	≥19
38-39	≥20

Number of Subjects Treated	Incidence
40-41	≥21
42-43	≥22
44-45	≥23
46-48	≥24
49-50	≥25
51-52	≥26
53-54	≥27
55-57	≥28
58-59	≥29
60-61	≥30
62-64	≥31
65-66	≥32
67-68	≥33

Note: No stopping boundaries for less than 6 JCAR017-Treated subjects. The enrollment will be paused if the boundaries are crossed, e.g. out of 10 JCAR017-Treated subjects, at least 7 subjects experienced specified toxicity events.

12. HEALTH-RELATED QUALITY OF LIFE/PATIENT-REPORTED OUTCOME ANALYSIS

12.1. Quality of Life Outcomes

EQ-5D-5L, EORTC QLQ-C30 and FACT-Lym "Additional concerns" subscale will be used to assess the subject's global health status, physical, social, emotional, and functional well-being as well as lymphoma-related quality of life. A valid assessment actually received for the EORTC QLQ-C30, EQ-5D-5L health utility, and EQ-5D VAS at a given assessment visit will be defined as: 1) at least one subscale of EORTC QLQ-C30 subscales being completed; 2) all five items of the EQ-5D-5L being completed; and 3) no missing EQ-5D VAS value at the corresponding visit, respectively. The FACT-LymS will be scored if more than 50% (ie, a minimum of 8) of the 15 items are answered, otherwise it will be set to missing.

The earliest available Health-Related QoL assessment prior to initial JCAR017 infusion will be the baseline for each subscale of the QoL analysis.

12.1.1 EORTC QLQ-C30

For EORTC QLQ-C30, all scales and single items are scored on categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life scale representing higher levels of global health status/quality of life and higher scores for a symptom scale representing higher level of symptoms. For the purpose of this analysis, the following subscales are selected as primary domains: global health/QoL, physical functioning, cognitive functioning, and fatigue.

In the absence of any officially recommended set of within-person change threshold (i.e., responder definitions or RDs), in this study, the RDs estimated by Osoba et al (1998) will be used for within-person changes: for improvement, +10 for all functioning and global QoL scales and -10 for all symptom scales; for deterioration, -10 for all functioning and global QoL scales and +10 for all symptom scales. The same values will be used as minimal important differences (MIDs) for within-group changes.

12.1.2 EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Herdman, 2011; EuroQol, 1990; Aaronson, 1993). The EQ-5D-5L has 2 components: a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels including "no," "slight," "moderate," "severe," and "extreme" or "unable to." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Accordingly, the vectors 11111 and 55555 represent the best health state and the worst health state,

respectively, described by the EQ 5D 5L. Altogether, the instrument describes 55 = 3,125 health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index measuring the value to society of his or her current health. In addition, the EQ-5D-5L VAS allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health. Thresholds for meaningful change for the EQ-5D-5L utility index and VAS in cancer patients have not been defined. The EQ 5D 5L is available in more than 130 languages. In this study, the UK (crosswalk) values set will be used.

For UK submissions, NICE currently recommend scoring EQ-5D-5L data using the mapping algorithm developed by van Hout et al (2012). For the EQ-5D-3L index scores (to which crosswalk EQ-5D-5L scores are most comparable), +0.08 for improvement and -0.08 for deterioration will be used as both the MIDs and RDs for the crosswalk EQ-5D-5L index score (Pickard, 2007).

12.1.3 FACT-LymS

The FACT-Lymphoma (FACT-Lym) is a standardized measure of HRQoL specific to patients with non-Hodgkin Lymphoma (Hlubocky, 2013). For this trial, only the FACT-Lym "Additional Concerns" subscale (FACT-LymS) was included in the study.

The FACT-LymS consists of 15 items. Each item is rated on a 5-point Likert scale ranging from 0 (Not at all) to 4 (Very much) (Hlubocky, 2013). The instrument will be scored according to the developers' guidelines (Webster, 2003; FACIT, 2010). Negatively worded items are reverse scored by subtracting the item response from 4 so that higher scores for each item, and for the subscale score, correspond to a better HRQoL. The FACT-LymS subscale score (range from 0-60) is calculated as the sum of individual item scores.

The MID for the FACT-LymS score ranges from 3 to 5 points (Hlubocky, 2013). There are no established within-person thresholds for the FACT-LymS; therefore, the score change of 3 (+3 for improvement and -3 for deterioration) will be used as both the within-group and within-person thresholds.

The analyses of the questionnaires will be based on the PRO analysis set. The following descriptive analyses are planned:

- Baseline scores, post-baseline scores, and change from baseline will be provided on global domain and sub-domains (as applicable); A line graph summarizing the mean changes from baseline will be produced for the primary subscales of interest.
- Count and percentage of subjects with minimal clinical benefit from baseline at each assessment time point;
- Count and percentage of subjects improving, with no change, and worsening their baseline score at each assessment time point;

- Completion rates of responses to the questionnaire, defined for each questionnaire as the proportion of valid assessments actually received out of the expected number (i.e., number of subjects in the study at each visit).

Reasons for missing questionnaires will be captured so that the appropriate imputation method can be applied according to questionnaire guidelines.

12.2. Hospital Resource Utilization

A summary of hospital resource utilization (all inpatient stays from the infusion of JCAR017 up to the earlier date of 24 months post the JCAR017 infusion or start of new anticancer therapy) will be provided for the JCAR017-treated analysis set. Description of each parameter below will be presented.

· Number of hospitalizations

· ICU inpatient stay (days)

· Non-ICU inpatient stay (days)

Duration of hospitalization for each stay (in days) = date of discharge – date of admission + 1.

For each subject, ICU and non-ICU inpatient stay are the sum of duration of all ICU and non-ICU stays respectively.

Supportive by-subject listing will be provided.

13. INTERIM ANALYSIS

Not Applicable

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

Table 7. SAP Summary of Changes

Revision Date	Section(s)	Summary of Revision	Reason for Revision
11 September 2020	4.4	Increase the sample size from at least 56 to approximately 62.	The hypothesis-testing pooled analysis will be based on a sample size of 80 patients from Study 017006 and BCM-001 Cohort 2. This change to the Study 017006 sample size allows flexibility in the number of patients included from Study 017006 and BCM-001 Cohort 2
11 September 2020		Change timing of the primary analysis from at least 6 months of follow-up to at least one post baseline response assessment.	The primary efficacy analysis is on overall response rate, which does not require 6 months of follow up to determine. All patients will be followed for efficacy for 2 years or until death, disease progression, or withdrawal from study, and the results summarized at the time of final analysis.
11 September 2020	10.3.3, 11.1.4	Included long term follow-up data for overall survival, deaths and long-term AEs.	Long-term follow-up data will be integrated in the study CSR for selected analysis.
11 September 2020	10.4	Added a section for sensitivity analysis.	Centralize items for sensitivity analysis.
11 September 2020	10.5	Removed TNE criteria and add HCT-CI and aaIPI for subgroup analysis.	To align with Protocol Am 5.
11 September 2020	10.3.5	Provided detailed descriptions of Pharmacokinetic and Pharmacodynamics Analyses	Instead of having a separate SAP, descriptions of PK and PD analysis are added to the study SAP per current practice in the liso-cel program.
11 September 2020	12	Provided detailed description of PRO analysis	Instead of having a separate SAP, descriptions of PRO analysis are added to the study SAP per current practice in the liso-cel program.
01 Jul 2021	2 10.1	Updated hypothesis testing of ORR to be based on 017006 data alone instead of the pooled 017006 and BCM-001 Cohort 2 data	[redacted]
01 Jul 2021	4.4 10.2.1	Updated sample size from ~80 based on the Pooled data to approximately 62 for 017006 itself	[redacted]
01 Jul 2021	10.2.1	Updated timing of primary analysis from approximately 80 subjects in total (pooled from 017006 and BCM-001	[redacted]

		Cohort 2) have been treated and followed for at least one post baseline response assessment to approximately 62 subjects have been treated and followed for at least 6 months of follow-up after first response	
01 Jul 2021	7 8.5.3 11.1	Added summary of COVID-19 related protocol deviation, con meds, AEs	[redacted]
01 Jul 2021	5.1	Added a table for nominal visit and visit window Clarified rules for selecting record for analysis/reporting when there are multiple records in a visit window	Added clarity regarding record selection, especially for laboratory test results.
01 Jul 2021	10.6	Added text for correlative analysis of PK parameters and select efficacy or safety endpoints	Provided high level summary of potential correlative analysis
01 Jul 2021	10.3.5.1 10.6.3 10.6.4	Added description of PVS to PK analysis section. Added description of RCL and PVS at occurrence of SPM as exploratory analysis	Addition of RCL, PVS, RCL and PVS in occurrence of SPM as long-term safety measure.
01 Jul 2021	16.4	Added primary and secondary estimand	[redacted]
14 Jul 2021	10.5	Added subgroup analyses	Added subgroups to align with other 2L studies and allow benefit-risk assessment in subgroups defined using age/organ function and disease status.

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16. APPENDICES

16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

16.1.1. Calculation Using Dates

Calculations using dates (e.g., subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (e.g, JCAR017) plus 1 day. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1

- Else use STUDY DAY = TARGET DATE – DSTART.

Note that Study Day 1 is the first day of treatment of study drug (JCAR017). Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7

- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4375

16.2. Date Imputation Guideline

16.2.1. Impute Missing Adverse Events / Prior or Concomitant Medications

A. Incomplete Start Date:

Missing day and month: the imputed day and month will be 01 Jan or the first dosing date if they have the same year, whichever is later;

Missing day only: the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.

Missing day, month, and year

- No imputation is needed, the corresponding AE will be included as TEAE.

B. Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month: the imputed day and month will be 31 Dec or the date of EOS if they have the same year, whichever is earlier;

Missing day only: the imputed day will be the last day of the month or the date of EOS date if they have the same month and year, whichever is earlier.

16.2.2. Impute Missing Initial Diagnosis Date

For partial diagnosis date, if the day and month are missing but the year is available, then the imputed day and month will be 01 Jul or the start date of the first prior anticancer treatment for disease under study if they have the same year, whichever is earlier. If the day is missing but the month and year are available, then the imputed day will be the first day of the month.

16.3. Select Clinical Laboratory Analytes

Table 7. Selected Clinical Laboratory Analytes

Laboratory Panel	Analytes
Hematology	• Hemoglobin (HGB) • Platelet count • Leukocytes • Absolute neutrophils count (ANC) • White blood cell counts (WBC) • Lymphocytes • Absolute lymphocytes count (ALC)
Chemistry	• Creatinine • Sodium • Total bilirubin • Direct bilirubin • Alanine aminotransferase (ALT; Serum glutamic pyruvic transaminase or SGPT) • Aspartate aminotransferase (AST; Serum glutamic oxaloacetic transaminase or SGOT) • Magnesium • Lactate dehydrogenase • Uric acid • Phosphate • Potassium • Calcium • Albumin
Coagulation	• Activated Partial thromboplastin time (aPTT) • International Normalized Ratio (INR) • Fibrinogen • D-dimer
Inflammatory markers	• C-reactive protein (CRP) • Ferritin
Immunoglobulins	• Immunoglobulin G (IgG) • Immunoglobulin M (IgM)

Laboratory Panel	Analytes
	• Immunoglobulin A (IgA)

16.4. Primary and Supplementary Estimand

Table 8. Primary Estimand

Estimand attribute	Primary definition		
Population	Adult R/R LBCL TNE patients who received JCAR017 infusion		
Treatment	JCAR017 infusion		
Endpoint	IRC-reviewed ORR, defined as the proportion of subjects with a BOR of either CR or PR based on the Lugano 2014 criteria. The BOR is the best disease response recorded from the JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy or JCAR017 retreatment. Proportion of subjects with a BOR of either CR or PR and 95% exact Clopper-Pearson confidence intervals will be provided.		
Intercurrent events	Event	Strategy	Rationale
	New anti-cancer therapy (including systemic therapy, HSCT, non-local radiation therapy)	While on treatment	Only response assessments prior to subsequent anticancer therapy or JCAR017 retreatment will be considered.
	Local radiation allowed per protocol	Treatment policy	Response assessments after local radiation will be considered
	Dropout or death without disease assessment	While on treatment	Included in the ORR analyses and categorized as non-responder
	Major protocol violations such as subjects found not meeting eligibility criteria after leukapheresis	Treatment policy	All subjects who received JCAR017 infusion and who was PET + pre-infusion and their response assessments after JCAR017 infusion will be considered.

Table 9. Supplementary Estimand

Estimand attribute	Supplementary definition		
Population	Adult R/R LBCL TNE patients who undergo leukapheresis		
Treatment	Leukapheresis + bridging therapy (if needed) + lymphodepleting chemotherapy + CAR-T infusion (including JCAR017 and non-conforming cell product)		
Endpoint	IRC-reviewed ORR, defined as the proportion of subjects with a BOR of either CR or PR based on the Lugano 2014 criteria. The BOR is the best disease response recorded from leukapheresis until disease progression, end of study, the start of another anticancer therapy or JCAR017 retreatment. Proportion of subjects with a BOR of either CR or PR and 95% exact Clopper-Pearson confidence intervals will be provided.		
Intercurrent events	Event	Strategy	Rationale
	New anti-cancer therapy (including systemic therapy, HSCT, non-local radiation therapy)	While on treatment	Only response assessments prior to subsequent anticancer therapy or JCAR017 retreatment will be considered.
	Local radiation allowed per protocol	Treatment policy	Response assessments after local radiation will be considered
	Dropout or death without disease assessment (including subjects who discontinued without receiving CAR T)	While on treatment	Responses prior to CAR T infusion not considered in analysis given adequate response assessments are not collected in the clinical database for subjects who discontinued without receiving CAR T. Subjects will be included in the ORR analyses and categorized as non-responder
	Major protocol violations such as subjects found not meeting eligibility criteria	Treatment policy	All patients and their response assessments after JCAR017 infusion will be considered.