Protocol for

Official Title of Study

A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting (TRANSCEND-OUTREACH-007)

NCT03744676

March 17, 2020

A SAFETY TRIAL OF LISOCABTAGENE MARALEUCEL (JCAR017) FOR RELAPSED AND REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (NHL) IN THE OUTPATIENT SETTING (TRANSCEND-OUTREACH-007)

Protocol Number:	017007 Amendment 2.0
Study ID:	TRANSCEND-NHL-007
NCT Number:	03744676
Date:	17 Mar 2020
Regulatory Sponsor:	Juno Therapeutics, Inc., a wholly-owned subsidiary of Celgene Corporation. 400 Dexter Ave North Suite 1200 Seattle, WA 98109 Phone: 206-582-1600 www.junotherapeutics.com
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Safety Reporting:	[redacted]

This trial will be conducted in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP, and applicable state, local, and federal regulatory requirements.

THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SYNOPSIS

Protocol Number: 017007

Protocol Title: A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting (TRANSCEND-OUTREACH-007)

Sponsor: Juno Therapeutics, Inc., a wholly-owned subsidiary of Celgene Corporation.

Study Rationale:

JCAR017 is a CD19-directed genetically modified autologous T-cell immunotherapy consisting of a defined composition of chimeric antigen receptor (CAR) T-cell product with flat dosing of both CD4+CAR+ and CD8+CAR+ T-cell subsets. Clinical trials of JCAR017 and other CAR T-cell products to date have been performed in tertiary care centers that have consolidated the site of care for CAR T-cell administration and follow-up. In the US, however, about 80% of patients receiving treatment for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in third line are treated outside of these centers. The product profile of JCAR017 is conducive to administration and monitoring in hospital outpatient clinics and cancer clinic networks; however, the safety profile of this product administered in nontertiary care centers has not been evaluated. Preliminary data from Juno Study 017001 show that treatment of this patient population with JCAR017 demonstrates encouraging efficacy results and a manageable safety profile, including low rates of severe cytokine release syndrome (CRS) and neurotoxicity (NT) events, which support outpatient administration and outpatient monitoring for toxicity. Early experience with JCAR017 in Study 017001 suggests that outpatient administration of JCAR017 can be provided safely with appropriate education and outpatient monitoring, and can reduce the duration of inpatient hospital stays by 40% when compared to inpatient administration (Maloney 2017). Thus, a safety study to assess the use of JCAR017 in nontertiary care outpatient settings is proposed to confirm these initial findings.

Study Objectives:

Primary:

- To evaluate the safety of JCAR017 administered in nontertiary care centers as reflected by Grade ≥ 3 adverse events (AEs) of CRS, NT, prolonged cytopenias, and infections in adult subjects with R/R aggressive B-cell non-Hodgkin lymphoma (NHL)

Secondary:

- To evaluate the overall safety and tolerability of JCAR017, including toxicity management and outcomes
- To evaluate the safety of JCAR017 treatment in subjects monitored as outpatients
- To assess the antitumor activity of JCAR017
- To assess the pharmacokinetic (PK) profile of JCAR017
- To assess health-related quality of life (HRQoL) and health economics and outcome research (HEOR)

Exploratory

- [redacted]

Study Design:

This is an open-label, multicenter, Phase 2 study to assess the safety and efficacy of JCAR017 administered in nontertiary care centers to adult subjects with R/R DLBCL, transformed DLBCL arising from indolent histologies (tDLBCL),high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B. There will be no control group in this study.

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A total of 114 subjects may be enrolled to ensure that approximately 80 subjects are treated with JCAR017, with a minimum of approximately 50 treated subjects monitored as an outpatient.

Upon enrollment, subjects will undergo leukapheresis to obtain lymphocytes for JCAR017 product generation. While JCAR017 is being manufactured and if required to control their disease, subjects may receive salvage low-dose chemotherapy or 1 cycle of noncurative standard-of-care antitumor therapy (ie, bridging therapy). Upon successful JCAR017 product generation, subjects will enter the treatment phase and will receive lymphodepleting chemotherapy with fludarabine and cyclophosphamide (flu/cy) followed by JCAR017 at a dose of 100×10^6 CAR T cells administered intravenously (IV) 2 to 7 days after completion of lymphodepleting chemotherapy.

After treatment with JCAR017, subjects will enter post-treatment follow-up, and will be followed on this study for up to 2 years for safety, PK and biomarkers, disease status, HRQoL, and survival, as described in more detail in the assessments sections below. Assessments for long-term safety, overall survival, and HRQoL will continue even after disease progression. After completing the 2 years of post-treatment follow-up 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 following the last dose of JCAR017.

Oversight

A Safety Review Committee (SRC), comprised of Principal Investigators, and the Sponsor's medical monitor, safety physician, and statistician will regularly assess the safety of JCAR017 administration throughout the trial. The SRC may make recommendations based on safety.

Study Population:

The target study population consists of adult subjects with R/R aggressive B-cell NHL who have failed at least 2 prior therapies.

Inclusion Criteria:

Subjects must meet all of the following criteria to be enrolled in this study:

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent prior to any study procedures
3. Relapsed or refractory B-cell NHL of the following histologies:

   DLBCL, not otherwise specified (NOS; includes biopsy-confirmed transformed DLBCL from indolent histologies), high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL and follicular lymphoma Grade 3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 systemic lines of therapy for DLBCL or after autologous hematopoietic stem cell transplant (auto-HSCT).
4. Positron-emission tomography (PET)-positive disease according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification"
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
6. Adequate organ function (must meet all), defined as:
   a. Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy
   b. Serum creatinine ≤ 1.5 × age-adjusted upper limit of normal (ULN), OR if greater than 1.5× ULN then calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min
   c. Alanine aminotransferase (ALT) ≤ 5 × ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)
   d. Adequate pulmonary function, defined as ≤ Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 dyspnea and oxygen saturation (SaO_2) ≥ 92% on room air

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e. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) scan performed within 1 month of the determination of eligibility

7. Adequate vascular access for leukapheresis procedure (either peripheral line or surgically placed line)
8. Subjects who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy
9. Females of childbearing potential* must:
   a. Have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and within 48 hours prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence** from heterosexual contact.
   b. Either commit to true abstinence** from heterosexual contact or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective method from screening until at least 12 months after the lymphodepleting chemotherapy.
   c. Agree to abstain from breastfeeding during study participation and for at least 12 months following lymphodepleting chemotherapy.
   d. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

   Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

   - Intrauterine device (IUD)
   - Hormonal (birth control pill, injections, implants)
   - Tubal ligation
   - Partner's vasectomy

10. Males who have partners of childbearing potential must:
    a. Practice true abstinence** or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for 12 months after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.
    b. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

    * A female subjects of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).

    **True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

11. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following lymphodepletion chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues, and cells for transplantation

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study)
2. History of prior allogeneic hematopoietic stem cell transplant (allo-HSCT)
3. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
4. History of another primary malignancy that has not been in remission for at least 2 years. The following are examples of exceptions from the 2-year limit: nonmelanoma skin cancer, definitively-treated stage 1 solid tumor with a low risk of recurrence, curatively-treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on a Papanicolau smear
5. Subjects with a history of or active human immunodeficiency virus (HIV) are excluded
6. Subjects with active hepatitis B, or active hepatitis C are also excluded. Subjects with a negative PCR assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy
7. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate anti-infection treatment at the time of leukapheresis or JCAR017 administration
8. Presence of acute or chronic graft-versus-host disease (GVHD)
9. History of any 1 of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association, cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
10. History or presence of clinically relevant CNS pathology such as epilepsy/seizure, paresis, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
11. Pregnant or nursing women. NOTE: Women of reproductive potential must have a negative serum pregnancy test performed within 48 hours of starting lymphodepleting chemotherapy
12. Use of any of the following:
    a. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids are permitted.
    b. Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m^2) given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy.
    c. Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) within 1 week of leukapheresis. Oral chemotherapeutic agents, including lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis.
    d. Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) within 2 weeks of leukapheresis
    e. Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
    f. Immunosuppressive therapies within 4 weeks of leukapheresis and JCAR017 administration (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti-IL6, or anti-IL6R)
    g. Donor lymphocyte infusions within 6 weeks of JCAR017 administration
    h. Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease (PD) in irradiated lesions or have additional nonirradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional nonirradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis.

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13. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or unwillingness or inability to follow the procedures required in the protocol
14. Prior CAR T-cell or other genetically modified T-cell therapy
15. Progressive vascular tumor invasion, thrombosis, or embolism
16. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

Study Sites: Subjects will be enrolled at multiple sites in the United States.

Drug Product, Dose, and Mode of Administration:

The JCAR017 drug product is a defined composition of autologous CD4+CAR+ and CD8+CAR+T cells that express a CD19-specific chimeric antigen receptor (CAR) and a truncated epidermal growth factor receptor (EGFRt) that are provided as frozen cell suspensions for IV administration at a flat dose. The JCAR017 drug product is provided as 2 individually formulated CD4+CAR+ and CD8+CAR+T-cell suspensions in media containing dimethyl sulfoxide for direct IV administration in equal CAR T-cell quantities.

JCAR017 is prepared at the site as 2 separate T-cell suspensions in syringes at doses of 50×10^6 CD8+CAR+ T cells and 50×10^6 CD4+CAR+ T cells (total dose of 100×10^6 CAR+ T cells) that are given IV in a single-dose schedule on Day 1 (between 2 and 7 days following the completion of lymphodepleting chemotherapy).

Duration of Study and Subject Participation:

The duration of study for each subject is up to 2 years, and the estimated total time for all subjects to complete the study is approximately [redacted] years.

Safety Assessments:

Adverse events/serious AEs (SAEs) and laboratory abnormalities (type, frequency, and severity) will be collected. Adverse events of special interest (AESIs) may include, but are not limited to, cytokine release syndrome (CRS), neurological toxicity (NT), prolonged cytopenia, Grade ≥ 3 infection, tumor lysis syndrome (TLS), macrophage activation syndrome (MAS), infusion reactions, and hypogammaglobulinemia, autoimmune disorder, and second primary malignancy (SPM).

Safety monitoring boundaries based on the incidence of Grade 3 or above JCAR017-related AESIs are established using a Bayesian framework to help detect safety signals during the course of the study. If the safety boundaries are crossed, enrollment will be paused and an ad hoc SRC meeting will be held to review the data. The study will remain paused for enrollment pending the SRC's recommendations.

Efficacy Assessments:

Tumor response will be assessed by diagnostic quality (with contrast) computed tomography (CT) scans (chest, neck, abdomen, and pelvis) and PET scans. Radiographic disease assessments will be performed pretreatment, at Day 29, and Months 3, 6, 9, 12, 18, and 24 months following the JCAR017 treatment or until disease progression. Bone marrow involvement by lymphoma will be assessed by PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response. Disease response and duration will be assessed by the Investigators according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014).

For subjects with suspected or confirmed CNS involvement, repeat cerebrospinal fluid (CSF) assessments by flow cytometry will be performed.

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Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments

[redacted]

Health-related Quality of Life and Health Economics and Outcomes Assessments

Quality-of-life outcomes will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EuroQol instrument EQ-5D-5L, which will be collected at specified timepoints throughout the study.

Information on hospitalizations and intensive care unit (ICU) admissions; and requirements for transfusions, IV immunoglobulin (IVIG), and growth factor support will be collected throughout the study and used to assess health economics and outcomes.

Statistical Methods:

The primary analysis is descriptive and will estimate the incidence of Grade ≥ 3 AEs of CRS, NT, prolonged cytopenias, and infections along with their 2-sided 95% exact Clopper-Pearson confidence intervals (CIs).

The type, frequency, and severity of AEs/SAEs, AESIs, and laboratory abnormalities and the overall incidence of any Grade ≥ 3 AEs will be summarized. Results will be presented using descriptive statistics. Median time to onset, median time to resolution of Grade ≥ 3 CRS and NT, and the use of tocilizumab and glucocorticoids for management of CRS and NT will be summarized using descriptive statistics. Safety analyses will be based on the JCAR017-Treated Analysis Set.

Objective response rate (ORR) and complete response (CR) will be summarized along with their 2-sided 95% exact Clopper-Pearson CIs. Duration of response (DOR), duration of complete response (DoCR), progression-free survival (PFS), and overall survival (OS) will be summarized using Kaplan-Meier methods. Efficacy analyses will be based on the JCAR017-Treated Analysis Set.

Pharmacokinetic data will be described and summarized using the Pharmacokinetic Analysis Set.

Changes in HRQoL outcomes will be summarized using descriptive statistics. Hospital resource utilization will be assessed based on the number of ICU and non-ICU inpatient days post-CAR T-cell infusion, the number of subjects transfused, the number of transfusions per subject, the number of subjects requiring growth factor support, and the number of subjects requiring IVIG support. Descriptive statistics for hospital resource utilization will be provided for subjects in the JCAR017-treated Analysis Set.

Justification for Sample Size:

Assuming a 30% drop out rate, a total of 114 subjects may be enrolled to ensure that approximately 80 subjects are treated with JCAR017, with a minimum of approximately 50 treated subjects monitored as an outpatient.

This study is designed for estimation and does not include formal hypothesis testing or adjustment for multiplicity. For any individual incidence rate (eg, AEs, ORR, CR), 80 subjects would provide a precision of ± 11.4% and 50 subjects would provide a precision of ± 14.5%, to estimate each endpoint assuming a confidence level of 95%. These are based on an event rate of 50% using the exact Clopper-Pearson method. Other rates would have narrower confidence intervals.

In Juno Study 017001, treatment with JCAR017 in subjects with aggressive B-cell NHL resulted in observed incidence rates for Grade ≥ 3 CRS/NT, infections, and prolonged cytopenias of 12%, 9%, and 38%, respectively (data on file). If similar rates are observed in this study, this would provide sufficient precision for meaningful interpretation of the observed rates.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	adverse event
AESI	adverse event of special interest
Allo-HSCT	allogeneic hematopoietic stem cell transplant
ASTCT	American Society for Transplantation and Cellular Therapy
AST	aspartate aminotransferase
AUC	area under the curve
Auto-HSCT	autologous hematopoietic stem cell transplant
ß-hCG	beta subunit of human chorionic gonadotropin
BCL2	B-cell lymphoma 2 gene
BCL6	B-cell lymphoma 6 gene
BOR	best overall response
BR	bendamustine plus rituximab
CAR	chimeric antigen receptor
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
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
DLBCL	diffuse large B-cell lymphoma
DMSO	dimethyl sulfoxide
DoCR	duration of complete response
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Term	Definition/Explanation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFRt	truncated epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	End-of-Study
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FiO_2	fraction of inspired oxygen
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
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
IB	Investigator's brochure
IBC	Institutional Biosafety Committee
ICF	informed consent form
ICH	International Council on Harmonisation
ICU	intensive care unit
IgA, IgG, or IgM	Immunoglobulin A, G, or M
IL-5, IL-6, or IL-10	Interleukin-5, 6, or 10
IL-6R	interleukin-6 receptor
IMID	immune modulating imide drug
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
JCAR017	lisocabtagene maraleucel
LDH	lactate dehydrogenase

Abbreviation or Term	Definition/Explanation
LN2	Liquid nitrogen
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MMSE	Mini-Mental State Examination
MUGA	multiple uptake gated acquisition scan
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NT	neurotoxicity
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PPDP	Protocol Product Deviation Plan
PT	preferred term
qPCR	quantitative polymerase chain reaction
R-CEOP	rituximab plus cyclophosphamide, epirubicin, vincristine, and prednisone
R-CEPP	rituximab plus cyclophosphamide, etoposide, procarbazine, and prednisone
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
R-Gem-Ox	rituximab with gemcitabine and oxaliplatin
RCL	replication-competent lentivirus
R-GDP	rituximab plus gemcitabine, cisplatin, and dexamethasone
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation or Term	Definition/Explanation
SaO_2	saturated oxygen
scFv	single chain variable fragment
sCRS	severe cytokine release syndrome
SD	stable disease
SOC	system organ class
SPD	sum of the perpendicular diameters
SPM	Second primary malignancy
SRC	Safety Review Committee
tDLBCL	transformed DLBCL from indolent histology
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
Tmax	time of maximum concentration
TMG	Toxicity management guidelines
TNF	tumor necrosis factor
ULN	upper limit of normal

1. INTRODUCTION

1.1. B-cell Non-Hodgkin Lymphoma

Approximately 72,000 new cases of non-Hodgkin lymphoma (NHL) will be diagnosed and approximately 20,000 patients will die of their disease in the United States in 2019 (Siegel 2019). NHL is the seventh most common cancer in the US, accounting for 4.2% of new cancers and 3.3% of all cancer-related deaths (SEER 2019). In the US, 80% to 85% of NHL cases are as B cell lymphomas and 15% to 20% are T-cell/natural killer cell lymphomas (NCCN 2019). Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive subtype, constituting approximately 30% of adult patients with NHL in the US, Europe, and Japan (Aoki 2008, Ferlay 2013, Novelli 2013, NCCN 2019). DLBCL is a disease of the elderly, with a median age at diagnosis of approximately 70 years (Issa 2015, Smith 2015), although it may rarely occur in children and young adults. With current treatments, relapsed or refractory (R/R) aggressive B-cell NHL have poor outcomes and the efficacy of salvage options are diminished in the era of rituximab-containing regimens. As such, there remains a need to develop new therapies for patients with R/R B-cell NHL.

Historically, first-line treatment for patients with high-stage aggressive B-cell NHL, including DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and follicular lymphoma Grade 3B, has been 6 or 8 cycles of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with reduced-intensity dosing regimens recommended for infirm or elderly patients > 80 years of age (NCCN 2019). Recently, data have been reported that support the use of more intensive therapy for PMBCL in the upfront setting (NCCN 2019), and ongoing studies are evaluating the effect of augmented RCHOP regimens on outcomes in high-risk subtypes of aggressive B-cell NHL.

Approximately one-third of DLBCL patients will be refractory to or relapse after R-CHOP therapy within 5 years of diagnosis (Cunningham 2013). Patients at high risk of relapse to R-CHOP include those with a high international prognostic index (IPI) score (Ziepert 2010, Cunningham 2013), those with activated B-cell or nongerminal center B-cell (GCB) origin (Fu 2008, Culpin 2013), and double-hit DLBCL, now referred to as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (Friedberg 2012, Morgan 2013). In these high-risk groups, 50% or less of patients are disease-free at 2 years (Ziepert 2010, Culpin 2013, Morgan 2013). Overall survival (OS) for all DLBCL patients approaches 75% at 5 years (Cunningham 2013); however, in high-risk patients, it may be as low as 25% to 30% (double-hit and non-GCB) to 50% (IPI 3 to 5) at 5 years (Ziepert 2010, Culpin 2013, Morgan 2013).

For patients who are refractory to or relapse following front-line therapy and are eligible for autologous hematopoietic stem cell transplant (auto-HSCT), various high-dose, platinum-based salvage chemotherapy regimens are recommended (NCCN 2019). It is estimated that 35% to 50% of R/R patients are not suitable for high-dose chemotherapy, for reasons including (but not limited to) comorbidities, poor performance status, or age, and are thus not eligible for HSCT. These patients may be treated with a platinum and/or gemcitabine-based regimen such as rituximab, or gemcitabine and oxaliplatin (R-GemOx), which may be combined with involved field radiation therapy (El Gnaoui 2007), or preferentially be enrolled in clinical trials testing the activity of novel drugs or combinations of agents. The effectiveness of single-agent or combination therapies is limited to a minority of those treated.

There are 2 Food and Drug Administration (FDA)-approved treatment as a salvage regimen for patients with R/R aggressive large B-cell NHL after at least 2 prior therapies- axicabtagene ciloleucel and tisagenlecleucel (discussed further below). Because these therapies were recently approved (2017), most data on outcomes in this population are from patients treated with combinations of agents or monotherapy or experimental therapies in clinical trials based on institutional preferences. The most commonly used treatment is a combination of rituximab with bendamustine (~25%) (Crump 2017). The effectiveness of combination and single-agent therapies for multiply relapsed, aggressive B-cell NHL is limited to a minority of those treated; specifically, the ORR (12% to 46%) and complete response (CR) rates (6% to 38%) are low; median PFS (< 6 months) and median OS (< 12 months) results are equally poor (Pettengell 2012, Rigacci 2012, Mounier 2013, Nagle 2013, Wang 2013, Czuczman 2014, Jacobsen 2015, Van Den Neste 2016). In a study of the most commonly used combination, rituximab and bendamustine, an ORR of 45% with a 15.5% CR was reported in patients with R/R DLBCL; median PFS was only 3.6 months (Vacirca 2013). Importantly, most patients in this study had only 1 prior therapy (median = 1, range = 1 to 9. Overall outcomes for patients who have relapsed after multi-agent salvage chemotherapy and auto-HSCT, or were refractory to salvage therapy and were not eligible for an auto-HSCT, are equally poor with median OS of 9.9 and 4.4 months, respectively (Nagle 2013, Van Den Neste 2016). In a recent meta-analysis of DLBCL patients who were refractory to their last chemotherapy-containing regimen or who relapsed within 12 months after auto-HSCT (the SCHOLAR-1 study), outcomes were even worse, with ORR of 26%, CR rate of 7%, and median OS of 6.3 months (Crump 2017). Therefore, there is significant unmet need for patients who have R/R B-cell NHL.

1.2. CD19 as a Therapeutic Target

CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells (Stamenkovic 1988). It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor (Stamenkovic 1988; Brentjens 2011).

CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (Li 1993, Li 1996, Davila 2012). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

1.3. CD19-Targeted Chimeric Antigen Receptors

CD19-specific chimeric antigen receptors (CARs) are single chain variable fragments (scFv) fused to a transmembrane domain and cytoplasmic signaling domains. Expression of the CD19-directed CARs in autologous T cells (CAR T) is achieved by ex vivo transduction using a recombinant retroviral or lentiviral vector. The CAR is expressed on the T-cell surface and redirects the transfected T cells to CD19-expressing lymphoma cells, leading to CD19-specific tumor cell recognition, lysis, cytokine secretion, and T-cell proliferation (Sadelain 2013). In clinical studies, CD19-targeted CAR T cells have demonstrated encouraging activity in adult and pediatric subjects with R/R B-cell acute lymphoblastic leukemia (ALL) and B-cell NHL (Porter 2011, Davila 2014a, Maude 2014, Kochenderfer 2015, Lee 2015, Park 2016, Turtle 2016a, Turtle 2016b, Turtle 2016c, Neelapu 2017, Schuster 2017).

Two CD19-directed CAR therapies have recently been approved by the FDA:

- Tisagenlecleucel, approved for the treatment of patients up to 25 years of age with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. (KYMRIAH™ [tisagenlecleucel] prescribing information, 2018).
- Axicabtagene ciloleucel, approved to treat adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (YESCARTA® [axicabtagene ciloleucel] prescribing information, 2019).

1.4. JCAR017 Drug Product

The final JCAR017 investigational drug product includes 2 individually formulated CD4+CAR+ and CD8+CAR+ T-cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and infused separately. JCAR017 is administered by intravenous (IV) infusion.

The CD19-specific CAR is introduced into autologous CD4+ and CD8+ T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (FMC63) and the 4-1BB and CD3ζ chain signaling domains. The truncated epidermal growth factor receptor (EGFRt) protein is expressed as a separate cell surface protein for purposes of cell tracking.

Please refer to the JCAR017 Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, clinical studies, and adverse event (AE) profile of JCAR017.

1.5. Clinical Experience with JCAR017

Clinical study 017001 is an ongoing open-label, multicenter, pivotal Phase 1 study to determine the efficacy and safety of JCAR017 in adults with R/R aggressive B-cell NHL, including DLBCL-NOS (de novo and transformed from indolent lymphoma), high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL histology, PMBCL, follicular lymphoma Grade 3B, and mantle cell lymphoma (MCL). Two disease-specific cohorts are being enrolled: the DLBCL cohort and the MCL cohort. Subjects in the DLBCL cohort must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have R/R disease after at least 2 lines of therapy or after auto-HSCT.

As of 12 April 2019, 255 subjects with DLBCL have undergone lymphodepletion chemotherapy with low-dose fludarabine (30 mg/m^2/day for 3 days) + cyclophosphamide (300 mg/m^2/day for 3 days) (flu/cy) and were treated with JCAR017 at Dose Level 1 (50×10^6 JCAR017 cells), Dose Level 2 (100×10^6 JCAR017 cells), or Dose Level 3 (150×10^6 JCAR017 cells) and were evaluable for efficacy. The best response was a CR in 53% of subjects in the efficacy analysis set treated at any dose regimen with efficacy data. Overall, in a total of 268 treated subjects, 42% of subjects experienced cytokine release syndrome (CRS), and 6 subjects (2%) had Grade ≥ 3 CRS (none

was Grade 5). Neurotoxicity (NT) was observed in 30% of subjects, including 10% with Grade ≥ 3 neurotoxicity (none was Grade 5) (Abramson, 2019).

See the JCAR017 IB for further details.

2. STUDY PURPOSE AND RATIONALE

The purpose of this Phase 2 study is to evaluate the safety and antitumor activity of JCAR017 administered in nontertiary care centers in adult subjects with R/R aggressive B-cell NHL who have failed 2 or more lines of therapy.

Clinical trials of JCAR017 and other CAR T-cell products to date have been performed in tertiary care centers that have consolidated the site of care for CAR T-cell administration and follow-up. In the US, however, about 80% of patients receiving treatment for R/R DLBCL in third line are treated outside of these centers (data on file). The product profile of JCAR017 is conducive to outpatient administration and toxicity monitoring in hospital outpatient clinics and cancer clinic networks with toxicity management in an associated hospital setting; however, the safety profile of this product administered in nontertiary care centers has not been evaluated.

Preliminary data from the ongoing Juno Study 017001 show that treatment of this patient population with JCAR017 demonstrates encouraging efficacy results and a manageable safety profile, including low rates of all grade and severe CRS and NT events. This supports outpatient administration and toxicity monitoring, with hospital admission upon symptoms of toxicity. Experience to date with JCAR017 in Study 017001 suggests that outpatient administration of JCAR017 can be provided safely with appropriate education and outpatient monitoring and can reduce the duration of inpatient hospital stays by 40% when compared to inpatient administration (Maloney 2017). Thus, a safety study to assess the use of JCAR017 in nontertiary outpatient settings is designed to confirm these initial findings.

2.1. Rationale for JCAR017 Dose Level

In Study 017001, JCAR017 at flat doses of 50×10^6 CAR+ T cells and 100×10^6 CAR+ T cells resulted in durable responses and demonstrated an acceptable safety profile in the third-line or greater treatment of R/R aggressive DLBCL.

Additionally, as of 09 Oct 2017, a trend toward improved ORR at 3 months was observed in patients treated at Dose Level 2 (100×10^6 CAR T+ cells) compared to Dose Level 1 (50×10^6 CAR+ T cells): 62% (16/26; 95% CI: 41, 80) versus 48% (19/40; 95% CI: 31, 64). Based on these results, the dose of 100×10^6 CAR+ T cells has been chosen for development in the third-line setting.

2.2. Rationale for Study Design

The purpose of this Phase 2 study is to evaluate the safety and efficacy of JCAR017 administered in nontertiary care centers in adult subjects with R/R aggressive B-NHL (non-Hodgkin's lymphoma) who have failed at least 2 prior lines of therapy. There is no approved standard of care for this population. A nonrandomized design was chosen because of the lack of effective therapies in this population (see Section 1.1), leading to concerns about comparing against an ineffective therapy given the promising preliminary efficacy results in third-line subjects (see

Section 1.5). Similarly, enrollment to a randomized study versus another assigned treatment is likely to be difficult, given the lack of efficacy of currently used regimens and the number of clinical studies ongoing in this population.

2.3. Rationale for Lymphodepleting Chemotherapy

As noted in Section 1.5, preliminary data available from subjects with R/R NHL in Study 017001 suggest that the low-intensity lymphodepleting chemotherapy regimen used, cyclophosphamide (300 mg/m^2/day × 3 days) combined with fludarabine (30 mg/m^2/day × 3 days) in combination with JCAR017, has adequate safety and good efficacy in subjects with R/R NHL. This lymphodepleting chemotherapy regimen was selected to limit toxicity and retain efficacy, as well as to optimize cellular expansion and efficacy after treatment with JCAR017. See the JCAR017 IB for more information. This same flu/cy dose is planned for the current 017007 study.

2.4. Rationale for Endpoints

The safety to be assessed in this trial are standard assessments for oncology clinical trials and are appropriate for monitoring the safety of patients in the study. Several AEs of special interest (AESIs) are defined for this study, including CRS, NT, prolonged cytopenia, Grade ≥ 3 infections, macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), infusion reactions, hypogammaglobulinemia, autoimmune disorders, and second primary malignancies because these events have been identified as potential risks associated with JCAR017 treatment as well as other CAR T-cell therapies.

The efficacy endpoints to be assessed in this study are standard endpoints for the assessment of aggressive B-cell NHL. Disease response will be determined according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014).

2.5. Risk/Benefit Summary

As discussed in Section 1.1, options for treatment of R/R DLBCL are limited and few patients respond to chemotherapy in the third-line setting and beyond. Preliminary data on JCAR017 treatment from the ongoing Juno Study 017001 show that treatment of this patient population with JCAR017 demonstrates encouraging efficacy results and a manageable safety profile, including low rates of all grade and severe CRS and NT events, which support outpatient administration and toxicity monitoring.

Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Unique NT events have also been reported and may include neurologic symptoms such as altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. In Study 017001, these toxicities have generally been found to be manageable and reversible. Guidance regarding management of other safety events is provided in Section 7. A detailed management algorithm for the assessment and treatment of signs of CRS and NT is provided in [redacted]

Experience with JCAR017 to date in Study 017001 further suggests that outpatient administration of JCAR017 can be provided safely with appropriate education and outpatient

monitoring for toxicity with hospitalization and inpatient toxicity management when required; this strategy can reduce the duration of inpatient hospital stays by 40% when compared to inpatient administration (Maloney 2017).

Thus, a safety study to assess the use of JCAR017 in nontertiary outpatient settings has been designed to confirm these initial findings.

Overall, considering the poor prognosis in R/R subjects receiving third-line treatment and the potential for good responses with a manageable safety profile with JCAR017, the benefit/risk is considered to be positive in this population treated in nontertiary outpatient settings.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 1. Efficacy analyses will be based on response assessments according to the Investigators.

Table 1: Study Objectives and Endpoints

Objective	Endpoints
Primary	
To evaluate the safety of JCAR017 administered in nontertiary care centers as reflected by Grade ≥ 3 adverse events (AEs) of CRS, NT, prolonged cytopenias, and infections in adult subjects with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL)	• Incidence of CRS, NT, prolonged cytopenia and infection AEs Grade ≥ 3
Secondary	
To evaluate the overall safety and tolerability of JCAR017, including toxicity management and outcomes	• Type, frequency, and severity of all AEs and laboratory abnormalities • Incidence of Grade ≥ 3AEs • Median time to onset and median time to resolution of Grade ≥ 3 CRS and NT • Use of tocilizumab and glucocorticoids for management of CRS/NT
To evaluate the safety of JCAR017 treatment in subjects monitored as an outpatient	• Type, frequency, and severity of all AEs and laboratory abnormalities
To assess the antitumor activity of JCAR017	• Objective response rate (ORR [CR + partial response]) • CR rate • Duration of response (DOR) and duration of complete response (DoCR), each defined as the time from first response to progressive disease (PD) or death • PFS, defined as the time from infusion of JCAR017 to PD or death, whichever is earlier • OS, defined as the time from infusion of JCAR017 to the date of death

Table 1: Study Objectives and Endpoints (Continued)

Objective	Endpoints
To assess the pharmacokinetic profile of JCAR017	• Maximum concentration (Cmax), time to peak concentration (Tmax), area under the curve (AUC) and other relevant PK parameters of JCAR017 in blood as measured using qPCR
To assess health-related quality of life (HRQoL) and health economics and outcomes research (HEOR)	• Measurement of HRQoL changes as assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EuroQol instrument EQ-5D-5L. • Number of intensive care unit (ICU) inpatient days and non-ICU inpatient days and reasons for hospitalization • Number of subjects transfused and the number of transfusions per subject. • Number of subjects requiring growth factor support. • Number of subjects requiring intravenous immunoglobulin (IVIG) support
Exploratory	
[redacted]	[redacted]

AE = adverse event; CR = complete response; CRS = cytokine release syndrome; DOR = duration of response; DoCR = duration of complete response; HEOR = health economics and outcomes research; HRQoL = health-related quality of life; ICU = intensive care unit; NHL = non-Hodgkin lymphoma; NT = neurotoxicity; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; qPCR = quantitative polymerase chain reaction; R/R = relapsed/refractory.

4. STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, multicenter, Phase 2 study to determine the safety and efficacy of JCAR017 in subjects who have R/R aggressive B-cell NHL who will be treated in the outpatient setting. Subjects will be treated with JCAR017 after completing lymphodepleting chemotherapy. There will be no control group for this study.

A total of 114 subjects may be enrolled to ensure that approximately 80 subjects are treated with JCAR017, with a minimum of approximately 50 treated subjects monitored as an outpatient.

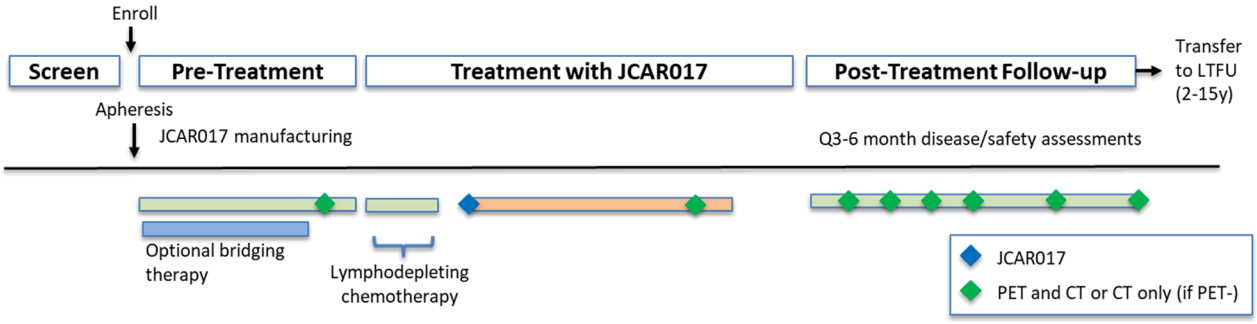
A schematic of treatment for each subject is provided in Figure 1. Subjects will undergo leukapheresis to collect peripheral blood mononuclear cells to enable JCAR017 product generation. Subjects who commence leukapheresis are considered enrolled on the day of leukapheresis. While JCAR017 is being manufactured and if required to control disease, subjects may receive salvage low-dose chemotherapy or 1 cycle of noncurative standard-of-care antitumor therapy as described in Section 8.2.2.

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

After completion of JCAR017 treatment, subjects will enter post-treatment follow-up, and will be followed on this study for 2 years for safety, disease status, health-related quality of life (HRQoL), and survival, as described in more detail in Section 8. 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 after JCAR017 treatment.

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 adverse events of special interest (AESI) will be established using a Bayesian framework (Thall 1994) as described in Section 10.3.5.4 and the statistical analysis plan. If the safety boundaries are crossed, enrollment will be paused and an ad hoc SRC will meet to review the data. The study will remain paused for enrollment pending the SRC's recommendations.

Figure 1: Study Schema for Individual Subjects



CT = computed tomography; LTFU = long-term follow-up; PET = positron-emission spectroscopy.

4.2. Study Duration and Duration of Subject Participation

The duration of study for each subject is up to 2 years and the estimated total time for all subjects to complete the study is approximately [redacted] years. All subjects who receive JCAR017 will be eligible to enroll in the LTFU protocol after completion of this study (see Section 8.2.10.).

4.3. Study Completion

A subject is considered to have completed the study if he/she has completed the last scheduled visit shown in the Schedule of Evaluations (see Appendix A).

The end of the study is defined as the date of the last scheduled assessment shown in the Schedule of Evaluations for the last subject in the trial.

4.4. Study Oversight

A Safety Review Committee (SRC), comprised of Principal Investigators and the Sponsor's medical monitor, safety physician, and statistician, will regularly assess the safety of JCAR017 administration throughout the trial. The SRC may make recommendations based on safety.

4.5. Suspension or Early Termination of the Study

The study can be suspended or terminated at any time by the Sponsor, the FDA, or at the recommendation of the Investigational Review Board (IRB). Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Determination that the primary endpoint has been met
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator may be informed of additional procedures to be followed in order to ensure adequate protection of subjects. The Investigator will be responsible for promptly informing the IRB, other applicable regulatory committees, and study subjects of the suspension or early termination of the trial, including the reasons for suspension or termination and any other regulatory committee, as applicable.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed to the satisfaction of the Sponsor, IRB, and/or FDA.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled in this study:

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent prior to any study procedures
3. Relapsed or refractory B-cell NHL of the following histologies:

   DLBCL NOS; includes biopsy-confirmed transformed DLBCL from indolent histologies, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, primary mediastinal B-cell lymphoma (PMBCL) and follicular lymphoma Grade 3B. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 systemic lines of therapy for DLBCL or after auto-HSCT.
4. Positron-emission tomography (PET)-positive disease according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
6. Adequate organ function **(must meet all)**, defined as:
   a. Assessed by the Investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy
   b. Serum creatinine ≤ 1.5 × age-adjusted upper limit of normal (ULN), OR if greater than 1.5× ULN then calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min
   c. Alanine aminotransferase (ALT) ≤ 5 × ULN and total bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with Gilbert's syndrome or lymphomatous infiltration of the liver)
   d. Adequate pulmonary function, defined as ≤ Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 dyspnea and oxygen saturation (SaO_2) ≥ 92% on room air
   e. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) scan performed within 1 month of determination of eligibility
7. Adequate vascular access for leukapheresis procedure (either peripheral line or surgically placed line)
8. Subjects who have received previous CD19-targeted therapy must have CD19-positive lymphoma confirmed on a biopsy since completing the prior CD19-targeted therapy
9. Females of childbearing potential* must:
   a. Have 2 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, and

within 48 hours prior to the first dose of lymphodepleting chemotherapy). This applies even if the subject practices true abstinence** from heterosexual contact.

b. Either commit to true abstinence** from heterosexual contact or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective method of contraception from screening until at least 12 months after receiving lymphodepleting chemotherapy.

c. Agree to abstain from breastfeeding during study participation and for at least 12 months following lymphodepleting chemotherapy.

d. There are insufficient exposure data to provide any recommendation concerning the duration of contraception and the abstaining from breastfeeding following treatment with JCAR017. Any decision regarding contraception and breastfeeding after JCAR017 infusion should be discussed with the treating physician.

Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy

10. Males who have partners of childbearing potential must:

a. Practice true abstinence** or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential for 12 months after lymphodepleting chemotherapy even if he has undergone a successful vasectomy.

b. There are insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

c. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals for at least 1 year following lymphodepleting chemotherapy. There are insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues, and cells for transplantation.

* A female subjects of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (ie, has had menses at any time in the preceding 12 consecutive months).
**True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5.2. Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from participation in this study:

1. Subjects with central nervous system (CNS)-only involvement by malignancy (note: subjects with secondary CNS involvement are allowed on study)
2. History of prior allogeneic hematopoietic stem cell transplant (allo-HSCT)
3. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis
4. History of another primary malignancy that has not been in remission for at least 2 years. The following are examples of exceptions from the 2-year limit: nonmelanoma skin cancer, definitively-treated stage 1 solid tumor with a low risk of recurrence, curatively-treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on a Papanicolau smear.
5. Subjects with a history of or active human immunodeficiency virus (HIV) are excluded.
6. Subjects with active hepatitis B, or active hepatitis C are also excluded. Subjects with a negative PCR assay for viral load for hepatitis B or C are permitted. Subjects positive for hepatitis B surface antigen and/or anti-hepatitis B core antibody with negative viral load are eligible and should be considered for prophylactic antiviral therapy.
7. Subjects with uncontrolled systemic fungal, bacterial, viral or other infection despite appropriate anti-infection treatment at the time of leukapheresis or JCAR017 administration
8. Presence of acute or chronic graft-versus-host disease (GVHD)
9. History of any 1 of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association, cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
10. History or presence of clinically relevant CNS pathology such as epilepsy/seizure, paresis, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
11. Pregnant or nursing women. NOTE: Women of reproductive potential must have a negative serum pregnancy test performed within 48 hours of starting lymphodepleting chemotherapy
12. Use of any of the following:
    a. Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days prior to leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, and inhaled steroids are permitted.
    b. Low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide $\leq$ 300 mg/m^2) given after leukapheresis to maintain disease control must be stopped $\geq$ 7 days prior to lymphodepleting chemotherapy.
    c. Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) within 1 week of leukapheresis. Oral chemotherapeutic agents, including

lenalidomide and ibrutinib, are allowed if at least 3 half-lives have elapsed prior to leukapheresis.

d. Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) within 2 weeks of leukapheresis
e. Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
f. Immunosuppressive therapies within 4 weeks of leukapheresis and JCAR017 administration (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as antitumor necrosis factor (TNF), anti-interleukin 6 (IL6), or anti-interleukin 6 receptor (IL6R)
g. Donor lymphocyte infusions within 6 weeks of JCAR017 administration
h. Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease (PD) in irradiated lesions or have additional nonirradiated, PET-positive lesions to be eligible. Radiation to a single lesion, if additional nonirradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis.

13. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or unwillingness or inability to follow the procedures required in the protocol
14. Prior CAR T-cell or other genetically modified T-cell therapy
15. Progressive vascular tumor invasion, thrombosis, or embolism
16. Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

5.3. Removal of Subjects from Treatment or Study

At the time of consent, subjects will be advised that they are free to withdraw consent from the study at any time for any reason; however, all subjects who have received treatment with JCAR017 will be encouraged to continue all study evaluations through the End-of-Study (EOS) visit as well as participate in the LTFU study. The Sponsor must be notified if a subject has withdrawn consent from the study or has requested to discontinue treatment, and the reason(s) must be documented.

5.3.1. Screen Failures

Screening failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study (Enrollment is described in Section 8.2.1). A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, eligibility criteria assessment, and any protocol procedure-related serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with a new subject number.

5.3.2. Subject Discontinuation Prior to Receiving Study Treatment

Subjects who undergo leukapheresis but do not receive lymphodepleting chemotherapy or JCAR017 will be followed for survival (see Section 8.2.9).

A subject's treatment may not occur for any of the following reasons:

- Subject did not receive study treatment due to disease-related complications
- Subject did not receive study treatment due to interim treatment-related toxicities
- Subject did not receive study treatment because the subject no longer meets eligibility criteria for other reasons (not related to disease or interim treatment)
- JCAR017 could not be manufactured
- Death
- Other

5.3.3. Subject Discontinuation from Further Study Treatment

In the rare event that a subject receives only a partial dose of JCAR017 (eg, CD8+CAR+ cells only), the subject should be reported as discontinuing treatment. Reasons for discontinuing treatment will include the following:

- Adverse event (AE)
- Investigator decision
- Subject decision
- Other

Subjects who are discontinued from treatment will not be withdrawn from the study. The subject will remain on study and continue to have all scheduled evaluations through the EOS visit per the Schedule of Evaluations (see Appendix A).

5.3.4. Subject Withdrawal from Study

A subject may be withdrawn from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by Sponsor
- Lost to follow up
- Death
- Other

See the Schedule of Evaluations in Appendix A for data to be collected at the EOS visit.

5.3.5. Replacement of Study Subjects

Subjects who sign the informed consent form but do not receive at least 1 dose of JCAR017 will be replaced. Subjects who receive nonconforming product (see Section 6.3.2) will be followed

per protocol, but will be excluded from certain analysis sets (as noted in Section 10.2) and will be replaced. All enrolled subjects will be assigned a unique subject number.

6. STUDY TREATMENTS

6.1. Leukapheresis

Following enrollment on the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCAR017 investigational product. Should a technical issue arise during the procedure or in the processing of the product such that it cannot be used for JCAR017 administration, the subject may have subsequent collection procedure(s) performed. Subjects must continue to meet eligibility requirements for repeat leukapheresis; see Section 8.2.3.1 for information about assessments that do not need to be repeated for additional apheresis.

Please refer to the PBMC collection manual for further details.

6.2. Anticancer Treatments between Leukapheresis and Lymphodepleting Chemotherapy

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being produced (ie, after leukapheresis and prior to lymphodepleting chemotherapy). Low dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide $\leq$ 300 mg/m^2) is allowed if completed at least 7 days prior to the start of lymphodepleting chemotherapy. If other agents are used, the washout periods noted in the exclusion criteria (see Section 5.2) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for DLBCL should be discussed with the Sponsor. Local radiation is allowed to a single lesion or subset of lesions if other un-irradiated PET-positive lymphoma lesions are present. If anticancer treatment is necessary during this time, the pretreatment PET and computed tomography (CT) assessments and other pretreatment study procedures (see Section 8.2.4) must be performed after the anticancer treatment has been completed. The subject must continue to have PET-positive disease and meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of lymphodepleting chemotherapy.

6.3. JCAR017 Investigational Drug Product

The JCAR017 investigational drug product is comprised of autologous CD8+ and CD4+ T cells that express a CD19-specific CAR that are provided as frozen cell suspensions for intravenous (IV) administration. The JCAR017 investigational drug product is provided as 2 individually formulated CD4+CAR+ and CD8+CAR+ T-cell suspensions in media containing DMSO for direct IV administration in equal CAR T-cell quantities into the subject.

The CD19-specific CAR is introduced into autologous CD8+ and CD4+ T cells ex vivo using a replication-incompetent, self-inactivating lentiviral vector. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (FMC63) and the 4-1BB and CD3ζ chain signaling domains.

See the JCAR017 Product Administration Manual for details of packaging and labeling, product tracking and accountability, and product disposal and destruction.

6.3.1. Protocol Product Deviation Plan

The JCAR017 Protocol Product Deviation Plan (PPDP) addresses the use of non-conforming investigational product in global clinical trials. The JCAR017 PPDP defines an assessment and decision-making process that permits release to the investigator and clinical site of drug product that does not meet the specification for certain non-safety related attributes (non-conforming JCAR017). In this process, the Celgene Medical Monitor and the Primary Investigator at the clinical site agree that the health of the subject and the risk/benefit profile is acceptable for the subject to receive treatment with the non-conforming investigational product. Development Quality Assurance then assesses the recommendation and is ultimately responsible for the drug product lot disposition. The JCAR017 PPDP is a standalone document.

6.3.2. Exception Use of Non-conforming Product

Once a decision is made for the exception use of non-conforming JCAR017, country specific requirements will be followed for the release of a non-conforming JCAR017 product to treat a subject enrolled in a JCAR017 clinical trial. For example, approval from local health authorities and/or IRBs/ECs will be obtained where required. Any subject will need to provide consent by signing the site's IRB approved non-conforming product ICF prior to receiving the non-conforming JCAR017 product. While subjects treated with non-conforming product will be followed as per the Table of Events (Appendix A) listed in the protocol, their data will be excluded from the primary safety/efficacy evaluable analysis. Their data will be analyzed separately (Section 10.2.4).

Subjects treated with non-conforming product will be replaced for the purposes of study enrollment of per protocol evaluable subjects.

6.3.3. Dose and Schedule

The dose of JCAR017 will be 100×10^6 CAR+ T cells. JCAR017 will be administered 2 to 7 days after completion of lymphodepleting chemotherapy, described in Section 8.2.5.2. Subjects must meet the criteria for treatment specified in Section 8.2.5.3.

6.3.4. Lymphodepleting Chemotherapy

Subject eligibility criteria must be confirmed immediately prior to starting the first cycle of lymphodepleting chemotherapy (see Section 8.2.5.1). The last dose of lymphodepleting chemotherapy must be administered 2 to 7 days before JCAR017 administration.

Subjects will be treated with fludarabine (30 mg/m^2/day for 3 days) plus cyclophosphamide (300 mg/m^2/day for 3 days) prior to treatment with JCAR017. The fludarabine dose should be reduced based on renal function. See Section 8.2.5 for the recommended schedule of administration and for the assessments that will be performed during lymphodepleting chemotherapy. Refer to the most recent package inserts for further details on administration of these agents.

Serum creatinine will be measured on the first day of lymphodepleting chemotherapy; chemotherapy should be withheld if serum creatinine is > 1.5 times the age-adjusted ULN OR calculated creatinine clearance (Cockcroft and Gault; Appendix C) or radioisotope glomerular filtration rate (GFR) is ≤ 30 mL/min. Delay of lymphodepleting chemotherapy by more than 14 days requires discussion with the Sponsor and may require rescreening (see Section 8.2.5.2).

Antiemetic therapy may be given prior to lymphodepleting chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

6.3.5. JCAR017 Premedication

Subjects should be pre-medicated with 650 mg acetaminophen PO and 25–50 mg diphenhydramine hydrochloride (PO or IV) 30–60 minutes prior to JCAR017 administration. These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Pre-medication with steroids is not allowed. See Section 6.6 for further guidance on steroid use and Section 7.5 for further information on infusion reactions.

6.3.6. JCAR017 Preparation and Cell Thawing

See the JCAR017 Product Administration Manual for details.

6.3.7. JCAR017 Administration

JCAR017 may be delivered in an outpatient setting at the Investigator's discretion. This setting is not recommended for the following subjects:

- Subjects who do not have adequate caregiver support
- Subjects who are staying greater than 60 minutes from the clinical trial site at the time of treatment.

Each JCAR017 dose consists of CD4+ CAR+ T cells and CD8+ CAR+ T cells, administered separately via IV. The subject must be continuously monitored during each IV administration of JCAR017. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured within 15 minutes prior to, and within approximately 15 minutes after the last IV administration, and then approximately every 15 minutes thereafter for the first hour, and hourly for the next 2 hours. If the subject's vital signs are not stable 4 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable.

Each T-cell suspension (CD8+ cells or CD4+ cells) must be thawed and the labeled dose volume administered into the subject within the specified expiration time after removal from shipping container or liquid nitrogen (LN2) freezer (if storing product on-site). If JCAR017 has been outside of the shipping container or LN2 freezer for longer than 2 hours, the product should be withheld, and the Sponsor study team immediately notified.

See the JCAR017 Product Administration Manual for complete information.

6.3.8. Acute Infusion Reactions

Acute infusion reactions may occur with administration of JCAR017. Guidelines for the treatment of acute infusion reactions are provided in Section 7.7.

6.4. Recommended Supportive Care, Additional Treatment, and Monitoring

Prophylactic treatment/measures are strongly recommended for subjects at risk for TLS, per institutional or clinical standards. Supportive care for the management of CRS is detailed in [redacted] In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe cytokine release syndrome (sCRS). Please refer to currently approved RoActemra® Summary of Product Characteristics (RoActemra SmPC, 2015). It is important to understand that the JCAR017 Management Guidelines for Cytokine Release Syndrome and Neurotoxicity and the recommended use of tocilizumab is different from the CRS management algorithms for the approved CAR Ts. The Sponsor requires that all JCAR017 sites must have at least 2 doses of tocilizumab available prior to infusion for each subject in the initial 30-day post-JCAR017 infusion period. If site utilizes more than one pharmacy facility, 2 doses of tocilizumab per subject are required in each pharmacy facility. It is recommended to resupply in case tocilizumab is given.

The preferred dose to intervene in subjects with sCRS is 8 mg/kg. Other anti-IL-6 antagonist should be considered in the event of sCRS not responding to tocilizumab. Dosing of any other anti-IL-6 agent should be per prescribing information.

Prophylactic treatment measures for neurological toxicities are detailed in [redacted]

The use of red blood cells and platelet transfusions, and/or colony-stimulating factors is permitted per institutional or clinical standards.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia prophylaxis [PJP], broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) is permitted per institutional standards.

Hospitalization may be required after treatment with JCAR017 to manage any treatment-associated toxicities. Subjects who do not have adequate support outside of the hospital or do not meet outpatient monitoring guidelines as per Section 8.2.5.5 should be considered for hospitalization during the initial monitoring period following JCAR017 treatment.

6.5. Concomitant Medications

Reporting periods for concomitant medications are summarized in Table 2. Management of potential risks is described in Section 7.

Table 2: Reporting Periods for Concomitant Medications

Reporting Period	What to Record/Report
Initial Informed Consent to first day of administration of lymphodepleting chemotherapy	Medications taken at the time of AEs/SAEs related to protocol-mandated procedures must be recorded/reported
From first day of administration of lymphodepleting chemotherapy to 90 days	All medications must be recorded/reported

Reporting Period	What to Record/Report
following last administration of JCAR017, or to EOS visit, whichever is earlier	

Table 2: Reporting Periods for Concomitant Medications (Continued)

Reporting Period	What to Record/Report
From 91 days following last administration of JCAR017 until EOS visit	Record/report the following: • Medications used at the time of AEs/SAEs related to JCAR017 and/or protocol-related procedures • Corticosteroids • Medications for the treatment of GVHD • Anticancer therapies

AE = adverse event; EOS = end of study; GVHD = graft versus host disease; SAE = serious adverse event.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfamethoxazole for pneumocystis pneumonia [PJP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) is permitted per institutional standards. Vaccination with an inactivated vaccine is permitted at any time in consultation with the medical monitor.

Subjects should be discouraged from using illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

For subjects receiving lymphodepleting chemotherapy but not JCAR017, concomitant medications associated with AEs/SAEs will be recorded for 30 days following the last dose of lymphodepleting chemotherapy.

Medications and transfusions given, and procedures performed for a pre-existing condition that is ongoing at LDC, should be reported as described in the CRF compliance guidelines (CCGs).

6.5.1. Medications Administered During Hospitalizations

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be used in the electronic case report form (eCRF). Therefore medications that should NOT be entered on the eCRF during inpatient and Intensive Care Unit (ICU) stays are defined in the CRF completion guidelines.

6.6. Prohibited Medications

Chemotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy.

The following medications are prohibited until the subject fails to respond, receives subsequent therapy for lymphoma, or 1 year has elapsed following JCAR017 treatment, whichever comes first:

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 20 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers.

- Steroids: therapeutic doses (> 20 mg/day of prednisone or equivalent) unless used for treatment of CRS or NT. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pretreatment containing steroids may be given for necessary medications (eg, intravenous immunoglobulin [IVIG]) after discussion with the Sponsor. Premedication with steroids for JCAR017 administration is not allowed. Physiologic replacement dosing of steroids is allowed. Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis are permitted.

The following medications are prohibited during the treatment and follow-up periods unless they are used as an anticancer agent after a subject fails to respond to JCAR017 or exhibits progression of their lymphoma:

- Donor lymphocyte infusion (DLI)
- Non-protocol specified anticancer agents. Lymphocytic cytotoxic chemotherapy may be administered as an extraordinary measure to treat AEs of uncontrolled JCAR017 proliferation, CRS, or neurotoxicity unresponsive to other therapeutic interventions
- Cetuximab, or other anti-epidermal growth factor receptor (EGFR) treatments, unless intended for treatment of uncontrolled JCAR017 proliferation or sCRS
- Experimental agents
- Radiation, unless needed for local control of a single tumor lesion in the presence of other nonirradiated PET-positive lesions

7. POTENTIAL RISKS AND MANAGEMENT OF TOXICITIES

A summary of management of potential treatment toxicity is provided below. See the JCAR017 IB for a complete discussion of potential risks associated with JCAR017. Cytokine release syndrome (CRS) and neurotoxicity (NT) are associated with CAR T-cell therapies. Celgene has developed specific toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs [redacted] These recommendations are based on the CRS revised grading system (Lee, 2014) and the CTCAE and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the eCRF to inform future modifications of the management guidelines.

7.1. Cytokine Release Syndrome

Administration of CAR T cells, such as JCAR017, is associated with CRS. Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS

are highly variable (Lee 2014), and management can be complicated by concurrent conditions. With JCAR017, CRS usually occurs within 2 weeks after infusion (Abramson 2017).

- Fever, especially high fever (≥ 38.5°C or ≥ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurotoxicity has been observed concurrently with CRS.
- CRS has been reported in a few cases to be associated with findings of MAS/hemophagocytic lymphohistiocytosis (HLH), and the physiology of the syndromes may overlap.

Please refer to [redacted] for a detailed description of CRS, grading, and treatment recommendations. If available and adopted as per site standard practice, CRS and neurological toxicity (NT) grading according to the ASTCT Consensus Grading System (Lee, 2019) should also be recorded in the eCRF to inform future modifications of the management guidelines.

7.2. Fever

The possibility of CRS should be considered for all subjects with fever (≥38.0ºC or ≥100.4ºF) following JCAR017 treatment. Subjects should be monitored closely for hemodynamic instability and changing neurologic status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly and managed per institutional or standard clinical practice.

The possibility of CRS should be considered for all subjects with fever following JCAR017 infusion. Subjects should be monitored closely for hemodynamic instability and changing neurologic status.

7.3. Neurologic Toxicities

CAR T-cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. With JCAR017 to date, the start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson 2017) after CAR T-cell infusion and, in severe cases, may require admission to the ICU for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.

Please refer to [redacted] for detailed descriptions of neurologic toxicities, grading, and treatment recommendations. Note: Tocilizumab is not indicated for the treatment of neurologic toxicities.

7.4. Macrophage Activation Syndrome

Macrophage activation syndrome is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages (See the JCAR017 IB for further background about MAS). Macrophage activation syndrome is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (Schulert, 2015). While there is considerable overlap in clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

Subjects treated with JCAR017 should be monitored for MAS, and cytokine-directed therapy should be considered as clinically indicated.

7.5. Infusion Reactions

Administration of JCAR017 may cause infusion reactions, including fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea. To minimize the risk of infusion reactions, all subjects should be premedicated with acetaminophen and diphenhydramine. In case a subject cannot tolerate diphenhydramine, an equivalent antihistamine may be substituted. Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and antiemetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR017 cells. Rigors may be treated with meperidine.

The following guidelines should be followed for infusion reactions:

Grade 1: administer symptomatic treatment; continue JCAR017 administration both CD8+CAR+ and CD4+CAR+ components at the same dose and rate

Grade 2: stop administration of JCAR017; administer symptomatic treatment; resume JCAR017 administration of both CD8+CAR+ and CD4+CAR+ components at a reduced rate only after symptoms resolve

Grade 3: stop administration of JCAR017, administer symptomatic treatment, and resume JCAR017 administration of both CD8+CAR+ and CD4+CAR+ components at a reduced rate of administration only after symptoms resolve. If a Grade 3 reaction recurs, discontinue JCAR017; no further CD8+CAR+ or CD4+CAR+ components of JCAR017 should be administered

Grade 4: discontinue administration of JCAR017 and administer symptomatic treatment as necessary; no further CD8+CAR+ or CD4+CAR+ components of JCAR017 should be administered

7.6. Tumor Lysis Syndrome

Both the lymphodepleting chemotherapy employed in this protocol and JCAR017 therapy have caused TLS in adult B-NHL subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia), and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment, including administration of allopurinol, rasburicase or equivalent, and hydration, per standard clinical practice.

7.7. B-cell Aplasia

B-cell aplasia is an expected potential off-tumor, on-target toxicity. Prolonged B-cell aplasia has been observed in other CD19-directed CAR T cell programs (Davila, 2014; Grupp, 2013). Serum immunoglobulin levels will be obtained from all subjects prior to and at various timepoints following JCAR017 infusion. Hypogammaglobulinemic subjects (serum IgG < 500 mg/dL) should be considered for IV immunoglobulin replacement therapy per institutional guidelines.

7.8. Cytopenias

Severe (Grade ≥ 3) cytopenias including anemia, leukopenia, neutropenia, and thrombocytopenia, can occur with JCAR017 and lymphodepleting chemotherapy and delayed recovery has been observed. Complete blood counts (CBCs) should be monitored after JCAR017 infusions until count recovery. Follow institutional guidelines in the event of Grade ≥ 3 cytopenias.

7.9. Infections

Life-threatening and fatal infections have been observed. Severe infections may include bacterial, fungal (including *pneumocystis jirovecii*), and viral infections (eg, CMV, HBV, respiratory viruses, and other viruses). A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, severe lymphopenia, and/or recent use of corticosteroids. Viral reactivation and other serious opportunistic infections should be considered in these settings, and prophylactic, pre-emptive, or symptomatic treatment with antimicrobial, antifungal, anti-pneumocystic, and/or antiviral therapies should be considered per local institutional guidelines.

7.10. Graft-versus-host Disease

The likelihood of GVHD occurring with CAR T-cell therapy is low, and while it remains a theoretical risk, it does not apply to patients enrolled in this protocol (exclusion criteria #2, 8). See the JCAR017 IB for further details.

7.11. Uncontrolled T Cell Proliferation

JCAR017 could theoretically proliferate out of control. If uncontrolled JCAR017 T-cell proliferation occurs, subjects may be treated with high-dose steroids (eg, methylprednisolone 1 to 3 g/kg/day, tapered over 1 week) or lymphodepleting doses of cyclophosphamide (1 to 3 g/m^2 IV). If an Investigator suspects uncontrolled proliferation of JCAR017-transfected cells, the Sponsor should be contacted immediately.

7.12. Replication-competent Lentivirus, Clonality, and Insertional Oncogenesis

Lentiviral vectors used in gene transfer are engineered to be replication-defective; however, generation of replication-competent lentiviruses (RCL) during manufacturing is still a possibility. Modern vector production systems have been improved to reduce the risk of RCL generation. To date, there have been no reports of RCL generated during lentiviral vector manufacturing, which may be due in part, to the use of self-inactivating vectors such as the lentiviral vector used in the production of JCAR017 (Rothe 2013).

Concerns for possible vector integration into the host genome have arisen due to preclinical studies that have shown retrovirus-mediated malignant transformation in mice (Li 2002, Modlich 2005) and monkeys (Donahue 1992), and a single clinical study reporting development of leukemia in subjects with X-linked severe combined immunodeficiency who received retroviral-modified CD34+ hematopoietic stem cells (Hacein-Bey-Abina 2003), including 1 subject who died (Couzin 2005). Of note, no instances of RCL generation during production or lentivirus-mediated malignant transformation in animals or humans have been reported to date.

Data has recently been published on the integration sites of retroviral and lentiviral vectors used for T-cell modification in clinical trials (Wang 2009, Scholler 2012, McGarrity 2013). No clonality of integration sites was observed. In addition, there did not appear to be enrichment of integration sites near genes involved in clonal expansion or persistence.

Per the FDA Recombinant DNA Advisory Committee guidelines (FDA 2000), all subjects will be followed in this study for RCL and vector sequences for up to 15 years following JCAR017 treatment as part of a LTFU protocol. All subjects will be monitored for evidence of unexpected JCAR017 expansion and the emergence of a new second primary malignancy (SPM), particularly one of T-cell origin. Investigators must contact the Sponsor immediately if an unexpected pattern of JCAR017 expansion and/or a new SPM arises.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any new malignancies, regardless of causal relationship to JCAR017, occurring throughout the subject's entire participation in the study. If a subject develops a new malignancy, the Sponsor will request that a tumor sample, and blood samples are collected (see 017001 laboratory manual). See Section 8.3.12.

7.13. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate lymphodepletion and CAR T-cell engraftment. Refer to the local package inserts for specific details surrounding the risks of fludarabine and cyclophosphamide.

8. STUDY ASSESSMENTS AND PROCEDURES

A Schedule of Evaluations is provided in Appendix A. Specific visits are described in Section 8.2 and descriptions of study assessments are presented in Section 8.2.11.

8.1. Schedule of Evaluations

There are 3 parts to this study: pretreatment, treatment, and post-treatment.

Pretreatment includes screening, leukapheresis, and pretreatment evaluation, and begins with assessing subject eligibility for study enrollment. If eligible, the subject will undergo leukapheresis as soon as possible, followed by pretreatment evaluation prior to lymphodepleting chemotherapy and JCAR017 administration. If needed, subjects may receive treatment between leukapheresis and lymphodepletion as described in Section 8.2.2.

All subjects will receive lymphodepleting chemotherapy prior to JCAR017. All subjects will be assessed for response at approximately Day 29.

Post-treatment includes safety and disease follow-up visits at approximately 2, 3, 6, 9, 12, 18, and 24 months after receiving JCAR017. The Month-24 visit will be the EOS visit.

8.2. Study Visits

8.2.1. Screening (Approximately 1 to 2 Weeks Prior to Leukapheresis)

The screening process begins when the subject signs the IRB-approved informed consent document and continues until the subject is determined to be eligible and the subject is enrolled, or until screen failure is determined. If a subject has had a screening procedure as standard of care within 30 days of consent, it may be used to evaluate study eligibility.

The following assessments will be performed during screening:

- Obtain informed consent (obtained any time before study-related procedures are performed).
- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met in order for subjects to continue in the study.
- Obtain medical history, including: disease diagnosis and history, HSCT history, chemotherapy, radiation and surgical history. If applicable, report/record history of toxicities related to prior treatments and allergies.
- ECOG performance status assessment (see [redacted]
- Physical examination (see Section 8.3.2)
- 12-lead electrocardiogram (ECG)
- ECHO or MUGA scan
- Local laboratory assessments (see Section 8.3.7):
  - Chemistries
  - CBC with differential
  - Viral serology
  - Serum beta subunit of human chorionic gonadotropin (ß-hCG) pregnancy test on women of child-bearing potential

- PET scan to confirm the presence of PET-positive lymphoma. PET scan may be performed longer than 30 days prior to screening if no intervening anticancer treatments have been performed.
- Subjects with transformed DLBCL from indolent histologies (tDLBCL) must submit a pathology report documenting that that their current relapsed disease is biopsy-confirmed tDLBCL
- If available, collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation.
- Record all AEs/SAEs related to protocol-mandated procedures and concomitant medications taken at that time (See Section 9.4.1 and Section 6.5, respectively)

8.2.2. Optional Bridging Therapy for Disease Control Prior to Lymphodepleting Chemotherapy

Subjects may undergo an optional cycle of salvage low-dose chemotherapy (eg, vincristine, rituximab, cyclophosphamide ≤ 300 mg/m^2) or noncurative standard-of-care chemotherapy for disease control prior to leukapheresis and/or while JCAR017 is being manufactured (ie, between leukapheresis and lymphodepleting chemotherapy). Examples of acceptable regimens include:

- Bendamustine plus rituximab (BR)
- Rituximab, cyclophosphamide, etoposide, procarbazine, and prednisone (R-CEPP)
- Rituximab, cyclophosphamide, epirubicin, and prednisone (R-CEOP)
- Rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP)
- Rituximab and lenalidomide

Other regimens may be acceptable after discussion with the Sponsor.

Any selected regimen should be administered per institutional guidelines. Chemotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy, and the washout periods noted in the exclusion criteria (see Section 8.2.3) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for DLBCL should be discussed with the Sponsor. If clinically indicated, local radiation is allowed to a single lesion or subset of lesions if other un-irradiated PET-positive lymphoma lesions are present.

If bridging anticancer treatment is given, subjects must continue to meet eligibility criteria pertaining to adequate organ function, active infections, pregnancy, washout of prior therapy prior to lymphodepletion, and PET-avid disease. If the subject has not had any cardiotoxic medications or radiotherapy in which fields include the heart, screening assessments of cardiac function (MUGA/ECHO) do not need to be repeated. The pretreatment evaluations in Section 8.2.4 noted as required after any intervening anticancer therapy must be repeated.

If lymphodepleting chemotherapy is delayed more than 14 days due to recovery from anticancer treatment, the subject must repeat eligibility assessments (some procedures may not be required after discussion with the Sponsor).

8.2.3. Leukapheresis (Approximately 4 Weeks Prior to JCAR017 Administration)

Following enrollment on the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of PBMCs for the production of the JCAR017 investigational product (See Table 3 for washout periods prior to leukapheresis). Should a technical issue arise during the procedure or in the immediate processing of the product such that it cannot be used for JCAR017 production, the subject may have subsequent procedure(s) performed (see 8.2.3.1).

Table 3: Washout Periods Prior to Leukapheresis

Drug	Washout
Alemtuzumab	6 months
Fludarabine	3 months
Cladribine	3 months
Radiation, multiple lesions	6 weeks
Experimental agents	4 weeks; or if no response or disease progression, then at least 3 half-lives
Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine)	2 weeks
Radiation, single lesion, if additional nonirradiated PET-positive lesions are present	2 weeks
Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent)	7 days
Cytotoxic chemotherapeutic agents not considered lymphotoxic (eg, doxorubicin, vincristine, gemcitabine, oxaliplatin, carboplatin, etoposide)	7 days
Rituximab	7 days
Oral chemotherapeutic agents (eg, lenalidomide and ibrutinib)	3 half-lives
Intrathecal (dexamethasone, methotrexate or cytosine arabinoside)	7 days

Leukapheresis should be scheduled as soon as possible after meeting eligibility requirements, in coordination with the Sponsor. Venous access is required for leukapheresis and should be determined according to institutional practice. The following assessments will be conducted:

- CBC with differential on the day of leukapheresis (or within 24 hours prior). CBC must include an absolute lymphocyte count.
- Vital signs (before and after leukapheresis)
- Cell collection through leukapheresis
- Record all AE/SAEs related to protocol-mandated procedures and concomitant medications taken at that time

8.2.3.1. Assessments Prior to Repeat Leukapheresis

If needed, subjects may undergo additional leukapheresis procedures if JCAR017 was unable to be manufactured. Subjects must continue to meet screening eligibility requirements in Section 5.1 and Section 5.2 in order to have a repeat leukapheresis collected. However, it is not

necessary to repeat PET scans, MUGA/ECHO, or ECG assessments to confirm eligibility. Positron-emission tomography/computed tomography scans will need to be repeated following the administration of optional bridging chemotherapy.

8.2.4. Pretreatment Evaluation (Prior to Lymphodepleting Chemotherapy)

Unless otherwise noted, pretreatment evaluations must be performed within 7 days prior to lymphodepleting chemotherapy.

The following assessments will be conducted:

- Confirm that the subject meets study eligibility criteria (see Section 5):
- ECOG performance status assessment
- Height/weight
- Physical examination
- Routine neurological exam
- Mini-Mental State Exam (MMSE) [redacted]
- Vital signs
- 12-lead ECG
- ECHO or MUGA scan (must be repeated after any intervening cardiotoxic anticancer therapy)
- Local laboratory assessments:
  - Serum ß-HCG pregnancy test on all women of child-bearing potential (within 48 hours prior to starting lymphodepleting chemotherapy.
  - Chemistries
  - CBC with differential
  - Coagulation
  - Inflammatory markers
  - Immunoglobulins
- Diagnostic quality CT (with contrast) performed at the study site. Must be done within 6 weeks of the start of lymphodepleting chemotherapy, and must be done after any intervening anticancer therapy, as close as possible to the start of lymphodepleting chemotherapy. Not required if done at the study site for screening within 6 weeks and no intervening anticancer therapy has been administered.
- PET scan performed at the study site. Must be done within 6 weeks of the start of lymphodepleting chemotherapy, and must be done after any intervening anticancer therapy, as close as possible to the start of lymphodepleting chemotherapy. Not required if done at the study site for screening within 6 weeks and no intervening anticancer therapy has been administered.

- Research blood samples (see the 017007 laboratory manual for details):
  - RCL testing
  - PK by quantitative polymerase chain reaction (qPCR)
  - Viral vector sequence testing by qPCR
  - Biomarkers
  - Immunogenicity Assessment
- Lumbar puncture or Ommaya reservoir tap for cerebrospinal fluid (CSF) assessment (required for subjects with suspected or confirmed CNS involvement only)
- MRI of the brain (required for subjects with suspected or confirmed CNS involvement or if clinically indicated)
- HRQoL questionnaires (QLQ-C30 and EQ-5D-5L)
- Record all AEs/SAEs related to protocol-mandated procedures and associated concomitant medications (see Section 6.5 and Section 9.4.1).

8.2.5. Lymphodepleting Chemotherapy Through Day 29

8.2.5.1. Criteria for Treatment

Subject eligibility criteria must be confirmed immediately prior to starting the first cycle of lymphodepleting chemotherapy. Low-dose chemotherapy or chemoimmunotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy.

Lymphodepleting chemotherapy will be withheld if serum creatinine is > 1.5 times the age-adjusted ULN OR calculated creatinine clearance (Cockcroft and Gault; [redacted] or radioisotope GFR is ≤ 30 mL/min. Delay of lymphodepleting chemotherapy of more than 14 days requires discussion with the Sponsor and may require rescreening.

Subjects should not experience a significant worsening in clinical status compared to either the initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with lymphodepleting chemotherapy or exclude them from treatment with JCAR017 (see Section 8.2.5.3).

8.2.5.2. Lymphodepleting Chemotherapy (Approximately 5 Days Prior to JCAR017)

Upon notification from the Sponsor that JCAR017 will be available, lymphodepleting chemotherapy should be initiated so as to finish 2 to 7 days prior to JCAR017 administration. Subjects will receive 3 days of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2).

The recommended administration is as follows:

1. The IV hydration is 1 L of 0.9% NaCl given at 500 mL/hr starting 2 hours prior to cyclophosphamide
2. Fludarabine 30 mg/m^2 IV over 30 minutes
    - If creatinine clearance is 50 to 70 mL/min: reduce each daily dose of fludarabine by 20%
    - If creatinine clearance is 30 to 49 mL/min: reduce each daily dose of fludarabine by 40%
    - Fludarabine should not be administered to subjects with CrCl < 30 mL/min.
    - Creatinine clearance (estimated glomerular filtration rate [eGFR] by Cockcroft-Gault, refer to [redacted] is required within approximately 48 hours of lymphodepleting chemotherapy to assess the need to adjust the dose of fludarabine. Indirect calculation of CrCl should be performed using the Cockcroft-Gault formula [redacted] Direct measurement of creatinine CrCl clearance is also acceptable.
3. Cyclophosphamide 300 mg/m^2 IV over 60 minutes
4. Additional 1 L of 0.9% NaCl given at 500 mL/hr

The following assessments will be performed on each day before administration of lymphodepleting chemotherapy:

- Vital signs
- Local laboratory assessments:
- Chemistries
- ECOG performance status (see [redacted]
- Record all AE/SAEs and concomitant medications (before, during, and after administration)

Antiemetic therapy may be given prior to lymphodepleting chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

8.2.5.3. Criteria for JCAR017 Treatment

Subject eligibility criteria must be confirmed immediately prior to administering JCAR017. Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of AEs associated with JCAR017 infusion. Subjects who meet at least 1 of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease

- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New-onset or worsening of other non-hematologic organ dysfunction Grade ≥ 3
- Taking any of the prohibited medications as described in Section 6.6.
- Progressive vascular tumor invasion, thrombosis, or embolism
- Venous thrombosis or embolism not managed on a stable regimen of anticoagulation

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCAR017 until the organ toxicities have recovered to Grade ≤ 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the Sponsor (see Section 6.3).

In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.

8.2.5.4. JCAR017 Administration–Day 1 (2 to 7 Days after Completion of the Last Dose of Lymphodepleting Chemotherapy)

JCAR017 should be delivered in an outpatient setting. At the Investigator's discretion, treatment can be delivered in an inpatient setting for the following types of subjects (see Outpatient Guidelines for further details):

- Subjects who do not have adequate caregiver support
- Subjects who are staying more than 60 minutes from the clinical trial site at the time of treatment
- Subjects with disease characteristics that, in the Investigators' clinical judgement, puts the subject at higher risk of complications (eg, TLS)
- Subjects with a psychosocial condition that puts them at risk for not following instructions

If changes to the JCAR017 manufacturing process are made, the Sponsor may mandate that subjects are treated in an inpatient setting until safety is confirmed.

Subjects must meet the criteria for treatment specified in Section 8.2.5.3.

The following evaluations will be performed before JCAR017 administration as indicated in the Schedule of Evaluations (see [redacted]

- Physical examination
- Weight
- ECOG performance status assessment

- Routine neurological examination
- MMSE [redacted]
- Clinical laboratory evaluations
  - Chemistries
  - CBC with differential count
  - Coagulation
  - Inflammatory markers
- Research blood samples (see the 017007 laboratory manual):
  - PK by qPCR
  - B-cell enumeration
  - Viral vector sequencing by qPCR
  - Biomarkers
- HRQoL
- Vital signs: will be measured within approximately 5 minutes (± 5 minutes) before and approximately every 15 minutes thereafter for the first hour and hourly (± 15 minutes) for the next 2 hours. Continue to monitor vital signs after this point until stable and as clinically indicated (see Section 8.3.3).
- Premedication: subjects should be premedicated with 650 mg acetaminophen by mouth (PO) and 25 to 50 mg diphenhydramine hydrochloride (PO or IV), 30 to 60 minutes prior to JCAR017 administration. In case a subject cannot tolerate diphenhydramine, an equivalent antihistamine may be substituted. These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids is not allowed (see Section 6.6).
- JCAR017 administration (2 to 7 days after completion of lymphodepleting chemotherapy)

8.2.5.5. Day 2 through Day 29

Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

Subjects can be followed in the outpatient setting after JCAR017 administration; however, they will require closer oversight for at least the first week. Subjects who have a high baseline tumor burden or high serum lactate dehydrogenase (LDH; ≥ 500 U/L prior to the start of lymphodepletion) have a higher risk for developing CRS and/or NT and should be closely monitored (see Section 7).

Subjects who are not appropriate candidates for outpatient monitoring include (see Outpatient Guidelines for further details):

- Subjects who do not have adequate caregiver support

- Subjects who are staying more than 60 minutes from the clinical trial site at the time of treatment (Day 2 to Day 29)
- Subjects with disease characteristics that, in the Investigators' clinical judgement, puts the subject at higher risk of disease-related complications (eg, TLS)
- Subjects with a psychosocial condition that puts them at risk for not following instructions

From Day 2 to Day 29, subjects will monitor their body temperature and record the value in a patient diary. Subjects will be instructed to take their body temperature 3 times per day (approximately every 6 to 8 hours) and at any time that they feel a subjective increase in body temperature and/or experience chills. In the event of a temperature of ≥ 38.0°C (100.4°F), subjects will be instructed to contact the study site immediately and seek medical evaluation.

Sites will monitor patients at least daily for 7 days (Day 2 to Day 8) by phone or with a clinic visit following administration for signs and symptoms of CRS and NT.

If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see [redacted] until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

8.2.6. Follow-up Period: Through Month 24

All subjects, including subjects who withdraw from treatment early and those with PD, will complete the post-treatment follow-up visits at approximately Months 2, 3, 6, 9, 12, 18, and 24 after the JCAR017 treatment for evaluation of safety, disease status, and survival.

Evaluations will be performed as indicated in the Schedule of Evaluations (see Appendix A).

8.2.7. Unscheduled Evaluations

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come in to the clinic for an unscheduled evaluation. The following assessments may be performed, as appropriate:

- Physical examination
- Vital signs
- ECOG performance status assessment
- MMSE (see [redacted] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE (see Section 8.3.3)
- Clinical laboratory evaluations
- PET scan
- CT/ magnetic resonance imaging (MRI) scan
- CSF assessment (see the 017007 laboratory manual)

- Research blood samples (see the 017007 laboratory manual):
  - PK by qPCR
  - Viral vector sequencing by qPCR.
  - Biomarkers
  - RCL

Additionally, if the Investigator requests any of the following procedures, research samples will be requested:

- CSF assessment
- Pleural, peritoneal, or other relevant fluid sampling
- Tissue sampling
- Autopsy

8.2.8. Assessments on Disease Progression/Relapse

The following assessments will be performed as soon as possible after disease progression/relapse:

- PET scan to confirm disease progression
- Bone marrow aspirate and biopsy, as clinically indicated (see the 017007 laboratory manual)
- Tumor biopsy, as clinically indicated (see the 017007 laboratory manual)
- HRQoL questionnaires (see Section 8.3.13)
- Research samples (see Section 8.2.7 and the 017007 laboratory manual)
  - PK by qPCR
  - B-cell enumeration
  - Viral vector sequencing by qPCR
  - Biomarkers

If a subject demonstrates early tumor progression (defined as occurring prior to/at 3 months after JCAR017 infusion), the Investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (see Section 8.3.1.1).

Any subsequent anticancer therapies administered for disease progression will be recorded as concomitant medications while the subject remains in long-term follow up, as described in Section 6.5. The results of any standard-of-care disease response assessments after these subsequent therapies will be collected as an unscheduled visit; this is part of the long-term follow up of disease status for 24 months after JCAR017 treatment (see Section 8.2.10).

8.2.9. Assessments in Subjects who Undergo Leukapheresis but Do Not Receive Treatment

The date of death for subjects who undergo leukapheresis but do not receive any further treatment on study should be collected in the eCRF.

8.2.10. Long-term Follow-up

Because this protocol involves gene transfer, post-treatment follow-up for lentiviral vector safety, disease status, and long-term survival will continue on this protocol until 24 months after JCAR017 treatment, regardless of disease status, and under a separate LTFU protocol for up to 15 years after JCAR017 treatment.

All subjects who either complete the post-treatment follow-up period specified in this protocol or who prematurely withdraw after a dose of JCAR017 will be asked to enroll in the LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the LTFU protocol. Subjects who discontinue early from this study and do not consent to participate in the LTFU protocol will be followed for survival through public record until their projected end of study visit.

8.2.11. Second Primary Malignancies Follow-up Period

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any new malignancies, regardless of causal relationship to JCAR017, occurring throughout the subject's entire participation in the study. If a subject develops a second primary malignancy, the Sponsor will request that a tumor sample (refer to 017007 laboratory manual) and blood samples are collected (See also Section 8.3.12.2 and Section 8.3.12.6).

8.3. Study Assessments

All study assessments should be performed at the times indicated in the Schedule of Evaluations in Appendix A.

8.3.1. Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluation at protocol-specified timepoints by diagnostic quality (with contrast) CT scans (chest, neck, abdomen, and pelvis) and PET scans. PET scans are not required after a subject achieves a CR unless progression is suspected on follow-up CT. Confirmation of PD and assessment of bone marrow involvement by lymphoma will be by PET scan only; bone marrow aspirates and biopsies will not be required for assessment of disease response. Upon documentation of disease progression or treatment with additional anticancer therapies, radiographic tumor evaluation is no longer required (Note, PET and CT scans will be read locally). Disease response will be determined according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson 2014) as described in [redacted] as well as other pertinent clinical data, as appropriate.

8.3.1.1. Pseudoprogression

If a subject demonstrates early tumor progression (defined as occurring prior to/at 3 months after JCAR017 infusion), the Investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare, which is a local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes) (Cheson 2014).

8.3.2. Physical Examination

A physical examination should include assessments of the following body parts/systems: abdomen, extremities, cardiovascular, pulmonary, neurological (see Section 8.3.3) and lymph node examinations. In addition, symptom-directed examinations should be performed.

8.3.3. Routine Neurological and Mini-Mental State Examinations

A routine neurological exam should include, at minimum, a physical exam to assess cranial nerves, motor and sensory skills, coordination and balance (see [redacted] In the event a subject experiences neurotoxicity, a Mini Mental State Examination (MMSE) should be done at time of onset of neurotoxicity and then daily until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE. The MMSE may be administered by an appropriately trained provider (ie, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment.

8.3.4. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry.

In addition, subjects will be required to monitor their body temperature at home and record it in a patient diary as described in Section 8.2.5.5.

8.3.5. Tumor Biopsy

At the time of disease progression or relapse if a tumor biopsy was obtained locally as part of standard-of-care procedures and tissue remains available, then either unstained slides cut from a FFPE block or the FFPE block itself will be submitted to the central laboratory.

If a subject develops a new or recurrent neoplasm other than the study indication, the Investigator will inform the Sponsor and, if available, collect a sample of the neoplastic tissue for assessment of RCL.

8.3.6. Adverse Events

Adverse events will be collected as described in Section 9.

8.3.7. Clinical Laboratory Evaluations

Screening and other laboratory evaluations (see Table 4) will be performed according to Appendix A. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs. See Section 9.3.2 for laboratory

abnormality AE reporting rules. The Investigator may choose to repeat any abnormal test in order to rule out laboratory or sample collection error.

Table 4: Analytes for Clinical Laboratory Evaluations

Laboratory Panel	Analytes
Chemistries	Glucose (fasting or nonfasting), BUN, creatinine, sodium, potassium, β2-microglobulin, chloride, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, CO_2, LDH, uric acid, triglycerides
Hematology	CBC with differential (manual or automated)
Coagulation	PT/aPTT, INR, fibrinogen, and D-dimer
Viral Serology	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb) Hepatitis C (Hep C antibody)
Serum Pregnancy	Serum ß-hCG pregnancy test
Inflammatory Markers	CRP, ferritin
Serum Immunoglobulins	IgG, IgM, IgA
CSF (if clinically indicated)	Protein, cell counts, glucose

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ß-hCG = ß subunit of human chronionic gonadotropin; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein: CSF = cerebrospinal fluid; HBcAb = hepatitis B core antibody; Hep C = hepatitis C virus; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; CRP = C-reactive protein; HIV = human immunodeficiency virus; IgA, G, M = immunoblobulins A, G, and M; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

8.3.8. ECOG Performance Status

ECOG performance status (see [redacted] will be used to evaluate subject eligibility at screening as specified in Appendix A.

8.3.9. MUGA/Echocardiogram

An assessment of LVEF will be performed by echocardiogram or MUGA to assess the cardiac function of the subject and to confirm study eligibility.

8.3.10. Electrocardiogram

A standard 12-lead ECG should be obtained. ECG tracings should be labeled with the study number, subject number, date, and Investigator's signature, and kept with the source documents at the study site.

8.3.11. Cerebrospinal Fluid Examination and Central Nervous System Symptom Assessment

Cerebrospinal fluid assessments and CNS imaging (MRI or CT) should be performed before and after JCAR017 administration for subjects with suspected or confirmed CNS involvement, and

as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS involvement by lymphoma exists).

Cerebrospinal fluid will be analyzed locally for cell count and differential cytology, and centrally for the presence of JCAR017 (see the 017007 laboratory manual for instructions on sending a sample for JCAR017 testing). CSF cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection. [redacted]

8.3.12. Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments

Testing and analysis of the samples will, generally, follow the Schedule of Evaluations in Appendix A. Allocation of samples to specific testing may be modified where sample material is limited; however, the total volume and type of material collected will not be modified beyond what is described in the laboratory manual.

Detailed information regarding the collection, handling, and shipment of samples for PK, pharmacodynamics, biomarker and immunogenicity assessments are provided in the 017007 laboratory manual.

8.3.12.1. Pharmacokinetic Assessments

JCAR017 PK in blood (and bone marrow, when available) will be assessed by qPCR.

8.3.12.2. Viral Vector Sequence Testing

Details regarding sample collection and processing are provided in the 017007 laboratory manual. The presence of vector sequences will be determined by evaluation of blood samples for the JCAR017 transgene by qPCR. If more than 1% of cells in test samples collected at the Month 12 visit or later test positive for vector sequences, the pattern of vector integration sites will be analyzed. If a predominant integration site is detected, then the subject will be asked to provide another blood draw 3 months later for follow-up testing.

If a subject develops disease recurrence or a SPM, the Sponsor will request a sample of the neoplastic tissue (see 017007 laboratory manual), and an unscheduled peripheral blood draw for RCL and viral vector sequence testing (see also Section 8.2.11).

8.3.12.3. Pharmacodynamic Assessments

Peripheral blood B-cell counts will be assessed to determine how JCAR017 impacts normal CD19+ B cells. In addition, levels of serum immunoglobulins will be monitored as another method to determine how normal B cells respond to treatment.

8.3.12.4. Biomarker Assessments

Biomarker assessments may be performed to evaluate JCAR017, tumor, and immune system characteristics that may be associated with JCAR017 safety and efficacy. The focus of these assessments would be to supplement biomarker findings discovered in previously conducted trials (eg, TRANSCEND NHL001) with JCAR017. These assessments may include cytokines and chemokines associated with CRS and NT, immune cell function, and tumor and tumor microenvironment characterization (only if a tumor biopsy is being obtained for clinical

purposes). Immunophenotypic and/or functional evaluation of JCAR017 and enumeration of immune cell subsets may also be performed. Peripheral blood and CSF (only if a lumbar puncture is indicated for clinical purposes) will be collected and banked for these evaluations.

Cytokines and chemokines may be measured in serum, plasma, and CSF (as available) as markers of immune activation. Potential correlations between cytokine/chemokine production and efficacy and severity of CRS and NT will be assessed.

Immunoregulatory pathways operative in the tumor microenvironment may influence the fate and function of adoptively transferred JCAR017 T cells. If a tumor biopsy is being obtained for clinical purposes and there is available tissue, assessment of specific cellular elements within the tumor and the tumor microenvironment will be performed on biopsy samples to correlate the presence of these factors with response, duration of response and/or JCAR017 persistence and function. This will include evaluation of JCAR017 infiltration and prevalence, markers of JCAR017 phenotype and function, and location of JCAR017 relative to CD19+ tumor cells. Immunosuppressive biomarkers on other cell types in the tumor microenvironment may also be assessed.

Flow cytometry will be performed to characterize the expansion and persistence of JCAR017 CAR T-cell subsets and to enumerate immune cell subsets in the blood, and if applicable, bone marrow and CSF. Analyses to detect tumor cells in peripheral blood and to analyze tumor cells by flow cytometry may also be performed. These studies aim to identify cellular markers associated with JCAR017 persistence as well as safety and efficacy.

Molecular profiling assessments, including single nucleotide polymorphism (SNP), ATACseq, AbSeq, targeted mutational analysis, whole exome/genome sequencing, and/or gene expression analysis (eg, RNA-Seq) may be conducted on JCAR017 cells, PBMCs and tumor cells in order to identify markers or signatures associated with clinical outcomes. Samples will be obtained pre-treatment, or isolated from peripheral blood, bone marrow aspirates, or tumor biopsies post-treatment as available.

Peripheral blood and tumor biopsies will be collected for these studies at the timepoints indicated in Appendix A.

Detailed information regarding the collection, handling, and shipment of biomarker samples is provided in the 017007 laboratory manual.

8.3.12.5. Immunogenicity Assessments

Immune responses to JCAR017 will be evaluated with an anti-therapeutic antibody (ATA) assay (plasma) to detect the presence of antibodies that bind to the extracellular region of JCAR017. In addition, cellular immunogenicity may be evaluated by testing PBMCs from subjects for the presence of anti-JCAR017 cytotoxic T cells.

8.3.12.6. Replication-competent Lentivirus Testing

Replication-competent lentivirus testing will be performed on genomic DNA obtained by a peripheral blood draw and, if positive, confirmed on PBMC, if available. Details regarding sample collection and processing are provided in the 017007 laboratory manual. Testing for RCL will use a polymerase chain reaction-based assay. Samples for RCL testing will be collected at the timepoints specified in Appendix A.

If all samples collected within the first year after the dose of JCAR017 are negative, subsequent samples will be collected and archived. However, if any of the samples are positive, the test will be repeated to confirm the result. If the repeat test is also positive, further analysis of the RCL will be undertaken in order to ascertain the nature of the RCL and potential effects. Subjects with detectable RCL are expected to continue to have blood samples collected and tested until RCL is undetectable. Any confirmed positive result from RCL testing will be reported as an SAE within 24 hours of the investigator being notified, and as an adverse experience in the form of an Investigational New Drug (IND) application safety report. Other relevant health authorities will be notified of the detected RCL in accordance with local guidelines.

Samples will be archived with appropriate safeguards to ensure long-term stability and an efficient system for the prompt linkage and retrieval of the stored samples with the subject's study records and the production lot records. Archived samples will be destroyed as outlined in the separate LTFU protocol.

If a subject develops a second primary malignancy, the Sponsor will request a sample of the neoplastic tissue (see 017007 laboratory manual), and an unscheduled peripheral blood draw for RCL and viral vector sequence testing (see Section 8.2.11).

8.3.13. Health-Related Quality of Life and Health Economics and Outcomes Research

Quality-of-life outcomes will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EuroQol instrument EQ-5D-5L. Subjects should, whenever possible, complete the questionnaires at the initiation of study visit, prior to any procedure or clinical evaluation. For subjects that do not complete the questionnaire at any given timepoint, reason for not collecting will be recorded (eg, too sick/unable to complete, administration error, subject refusal).

If the subject withdraws from the study prematurely, all attempts should be made to obtain final quality-of-life questionnaires prior to subject discontinuation.

8.3.13.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item scale composed of both multi-item scales and single-item measures. All of the scales and single-item measures range in score from 0 to 100. A higher scale score represents a higher level of well-being and better ability of daily functioning. Thus, a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/HRQoL represents a high HRQoL, but a high score for a symptom scale/item represents a high level of symptomatic problem.

8.3.13.2. EQ-5D-5L

EQ-5D 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. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems).

8.3.14. Hospital Resource Utilization

Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and the number of non-ICU inpatient days. Dates of and reasons for admission and discharge to the hospital and to the ICU will be collected on the appropriate eCRF. The number of subjects requiring packed red blood cell or platelet transfusions, the number of transfusions per subject, the number of subjects requiring growth factor support, and the number of subjects requiring IVIG support will be summarized from the information gathered on the appropriate eCRF.

9. SAFETY MONITORING AND REPORTING

9.1. Definitions

9.1.1. Adverse Event

In accordance with the International Council for Harmonisation (ICH) E2A guideline, and 21 Code of Federal Regulations (CFR) §312.32, an AE is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

9.1.2. Serious Adverse Event

An SAE is defined as an event that, at any dose, meets any of the criteria in Table 5. Special considerations for SAE reporting are presented in Table 6.

Table 5: Definitions of Serious Adverse Events

Criteria	Description
Fatal:	The AE resulted in death
Life-threatening:	The AE placed the subject at immediate risk of death (This classification does not apply to an AE that hypothetically might have caused death if it had been more severe).
Hospitalization/prolongation of Hospitalization:	The AE resulted in hospitalization or prolongation of hospitalization (See Table 6 below).
Disability/incapacity:	The AE resulted in a disability, significant incapacity, or substantial disruption of the subject's ability to conduct normal life functions
Congenital Anomaly/birth Defect:	The AE was an adverse outcome in a child or fetus of a subject exposed to the study treatment regimen before conception or during pregnancy
Medically Important:	The AE was a medically important event that did not meet any of the above criteria, but may have jeopardized the subject and may have required medical or surgical intervention to prevent 1 of the outcomes listed above (examples include allergic bronchospasm that required treatment in an emergency room, seizures that do not result in hospitalization, or blood dyscrasias)

AE = adverse event.

Table 6: Special Considerations for SAE Reporting

Criteria	Description
Hospitalization/prolongation of hospitalization Note: complications and/or prolonged admissions for routine treatment or procedures do require SAE reporting	This classification **does not** apply for the following hospitalizations: • Admissions for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) in the absence of any clinical AE • Admissions at the discretion of the investigator for administration of lymphodepleting chemotherapy or JCAR017 • Admissions for elective or preplanned treatment for a pre-existing condition that is unrelated to the condition under study and has not worsened since providing informed consent • Admissions for routine treatment (eg, platelet transfusion) or monitoring of the condition under study not associated with any deterioration in condition • Admissions for routine procedures (eg, bone marrow aspiration) associated with the disease under study • Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above

AE = adverse event; EOS = end of study; FDA = Food and Drug Administration; SAE = serious adverse event.

9.1.3. Adverse Events of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest may include, but are not limited to, CRS, NT, prolonged cytopenia, Grade ≥ 3 infections, TLS, MAS, infusion reactions, hypogammaglobulinemia, autoimmune disorders, and second primary malignancies (see [redacted] for CRS/NT). These events have been identified as potential risks associated with JCAR017 treatment as well as other CAR T-cell therapies. Details of the AESIs definitions are provided in the SAP.

Prolonged cytopenia (laboratory values), is defined as the occurrence of Grade ≥ 3 cytopenia not resolved by the Day 29 visit, based on laboratory results of low hemoglobin, absolute neutrophil count decreased, and platelet count decreased. The frequency of subjects experiencing each individual laboratory abnormality and the total number with at least 1 abnormality will be summarized, as will recovery from prolonged cytopenia after Day 29.

9.1.3.1. Grading and Intensity of Adverse Events

Adverse events, with the exception of CRS, will be graded using the CTCAE, Version 4.03 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). CRS will be graded according to the grading scale adapted from Lee (Lee 2014), [redacted]

The reported verbatim term should be the most descriptive medical diagnosis, even if it does not match the CTCAE term used for assigning severity.

AE severity and seriousness will be assessed independently. 'Severity' refers to the intensity of an AE, while 'serious' is a regulatory definition and serves as a guide to the Sponsor for defining regulatory reporting obligations.

9.2. Relationship to Study Drug

The assessment of the relationship of an AE/SAE to lymphodepleting chemotherapy and JCAR017 (related or not related) is a clinical decision based on all available information and the following considerations:

Related:	There is a reasonable possibility and/or evidence to suggest a causal relationship between the study drug and the AE/SAE and no other more likely alternative cause (concomitant drugs, therapies, disease complications, etc.) is suspected.
Not related:	There is no reasonable possibility and/or evidence to suggest a causal relationship between study drug and the AE/SAE and another more likely alternative cause (concomitant drugs or therapies, disease complications, etc.) is suspected.

9.3. Recording Adverse Events

Adverse events/SAE are recorded on the eCRF in accordance with the reporting criteria for different time periods as defined in Section 9.4. Each AE/SAE is to be evaluated for:

- Duration (onset and resolution dates)
- Severity, including grade changes during the 90-day period following JCAR017 administration, as per the eCRF completion guidelines (see Section 9.1.3.1)
- Outcome
- Seriousness (see Section 9.1.2)
- Causal relationship with lymphodepleting chemotherapy or JCAR017 (see Section 9.2)

9.3.1. Recording a Diagnosis versus Signs and Symptoms

Whenever possible, a unifying diagnosis should be reported, as opposed to a listing of individual symptoms. However, symptoms should be grouped into a diagnosis only if each sign or symptom is a medically confirmed component of that diagnosis as evidenced by current standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE/SAE.

One exception to reporting a diagnosis as opposed to symptoms is the event of CRS. If a subject experiences an event of CRS, a diagnosis of CRS and any grade changes for the event of CRS should be reported as an AE. Individual signs and symptoms of CRS and grade changes for those signs and symptoms should be entered as CRS Symptoms in the eCRF.

When manifestations of neurological toxicities appear in the presence of CRS or alone, those manifestations should be reported as separate AEs.

9.3.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Any laboratory abnormality (eg, clinical chemistry or hematology) or other abnormal assessment findings (eg, ECG or vital signs) that meets any of the following criteria should be recorded as an AE or SAE:

- Requires medical or surgical intervention (including transfusions or growth factors)
- Leads to product discontinuation, delay, or interruption
- Associated with clinical signs and/or symptoms
- Otherwise clinically significant as determined by the Investigator

The clinical diagnosis, rather than the laboratory result or CTCAE, should be reported by the Investigator (eg, anemia versus low hematocrit; neutropenia versus neutrophil count decreased).

9.3.3. Recording Serious Adverse Events

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in death should be recorded in the eCRF and reported on the SAE Report Form.
- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself.
- When progression of the disease under investigation meets any of the seriousness criteria, it will be reported as an individual SAE. When reporting SAE terms related to disease progression, specific manifestations of the progression (eg, "malignant pleural effusion," "lymphadenopathy from underlying non-Hodgkin lymphoma") should be reported, rather than the general term "disease progression."

9.3.4. Death Reports

All deaths must be reported on the Death eCRF. Deaths due to PD will not be reported as an SAE unless considered related to a study drug.

Any AEs leading to death from the time the subject provides informed consent through 90 days after the JCAR017 infusion should be reported according to Table 7.

Deaths that occur more than 90 days after JCAR017 infusion will be captured on the Death eCRF and reported as an SAE only if considered related to any study procedure or JCAR017.

9.3.5. Safety Queries

Queries pertaining to SAEs will be communicated from the Sponsor Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than ten (10) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

9.3.6. Pregnancy

All pregnancies or suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring at any time after

receipt of JCAR017, in a female subject or in the female partner of a male subject, must be reported to the Sponsor within 24 hours of learning of its occurrence The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

Pregnancy follow-up, including all perinatal and neonatal outcomes, should be recorded on a Pregnancy Follow-up Form and should be submitted to the Sponsor within 24 hours of awareness. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the "seriousness criteria" in Section 9.1.2, should be reported as SAEs.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will additionally request information about the mother and child's health during each trimester of pregnancy and for 1 year following the birth of the infant. Please reference the pregnancy information consent (permission) forms for data collection for additional information.

9.4. Reporting Adverse Events to the Sponsor

9.4.1. Reporting Periods for AEs and SAEs

Reporting periods for AEs and SAEs are summarized in Table 7.

Table 7: Reporting Periods for AEs and SAEs

Reporting Period	What to Record/Report
Initial Informed Consent to first day of administration of lymphodepleting chemotherapy	Only AEs/SAEs related to protocol-mandated procedures must be recorded/reported.
From first day of administration of lymphodepleting chemotherapy to 90 days following administration of JCAR017 or to EOS visit, whichever is earlier[a]	All AEs and SAEs, irrespective of causality, must be recorded/reported.
For subjects starting a subsequent nonchemotherapy-containing anticancer therapy (eg, checkpoint inhibitors, IMIDs) prior to 90 days following JCAR017 administration	All AE/SAEs will be collected after initiation of the subsequent therapy for 90 days following final JCAR017 infusion or 30 days following initiation of subsequent therapy, whichever is longer.
For subjects starting a subsequent chemotherapy-containing anticancer therapy prior to 90 days following JCAR017 administration	Only AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported after initiation of subsequent therapy.
From 91 days following administration of JCAR017 until EOS visit	All AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported.
From 91 days following administration of JCAR017 or start of subsequent chemotherapy, whichever is first, to EOS visit	The following conditions must be reported as SAEs, regardless of relationship to study drug: (as described in Table 6) • Second primary malignancies • New onset or exacerbation of a pre-existing neurologic disorder

Reporting Period	What to Record/Report
	• New onset or exacerbation of rheumatologic or other autoimmune disorder • New onset hematologic disorder (eg, myelofibrosis) Rare and unexpected disorders with and unknown etiology (eg, Guillain-Barré, Stevens-Johnson syndromes)

AE = adverse event; EOS = end of study; IMID = immune modulating imide drug; JCAR017 = autologous CD4+ and CD8+ T cells expressing a CD19-specific chimeric antigen receptor; SAE = serious adverse event.

[a] If a subject receives lymphodepleting therapy but not JCAR017, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy.

[b] Any clinically significant conditions/events unrelated to study procedures should be reported either in medical history or as an adverse event as described in the CCGs.

SAEs will be followed until they resolve or return to baseline; the event stabilizes or is no longer considered clinically significant by the Investigator; the subject dies or withdraws consent; or study closure. All nonserious AEs will be followed through the safety reporting period. Certain nonserious AESIs may be followed until they resolve, return to baseline, or study closure.

9.4.2. Reporting Timelines for Serious Adverse Events

All SAEs must be reported within 24 hours of the Investigator's knowledge of the event by facsimile or other appropriate method (eg via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the SAE form is completed in its entirety and that the data on the form is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to investigational product) recorded in the CRF [redacted]

The SAE Report Form should provide a detailed description of the SAE and include a concise summary of hospital records, discharge reports, and other relevant documents. If a subject died and an autopsy was performed, copies of the autopsy report and death certificates are to be sent to Celgene Drug Safety as soon as these become available. If a subject develops a second primary malignancy, copies of the pathology and histology reports are to be sent to Celgene Drug Safety as soon as these become available.

The Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 10 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10. STATISTICAL METHODS

More details will be provided in a separate statistical analysis plan (SAP), which will be finalized prior to database lock.

10.1. General Considerations

This study is designed for estimation and does not include formal hypothesis testing or adjustment for multiplicity. Data from all sites will be combined for the analysis. Data from subjects who received nonconforming product will be summarized separately.

10.2. Analysis Sets

10.2.1. Screened Set

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

10.2.2. Eligible Set

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

10.2.3. Leukapheresed Set

The Leukapheresed Set includes subjects who undergo leukapheresis.

10.2.4. JCAR017-treated Analysis Set

The JCAR017-treated Analysis Set will include all subjects who have received a dose of conforming JCAR017 cell product.

10.2.5. Outpatient Analysis Set

The Outpatient Analysis Set will include all subjects in the JCAR017-treated Analysis Set who are monitored as an outpatient. A subject is considered to be monitored as an outpatient if, following JCAR017 administration, the subject is monitored initially as an outpatient, regardless of JCAR017 administration setting.

10.2.6. Pharmacokinetic Analysis Set

The PK Analysis Set includes subjects in the JCAR017-treated Analysis Set who have the necessary baseline and on-study PK measurements to provide interpretable results for the specific parameters of interest.

10.3. Planned Analyses

10.3.1. Subject Disposition and Baseline Characteristics

Descriptive summaries of demographics and baseline characteristics will be presented for the JCAR017-treated Analysis Set and the Outpatient Analysis Set.

Available demographic and baseline information on such subjects will be listed and summarized.

10.3.2. Primary Endpoints

The primary endpoints of the study are:

1. Incidence of Grade ≥ 3 CRS, a syndrome which is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia
2. Incidence of Grade ≥ 3 NT, defined as an Investigator-identified AE considered neurotoxicity related to JCAR017
3. Incidence of Grade ≥ 3 prolonged cytopenias (laboratory values), defined as the occurrence of Grade ≥ 3 cytopenias not resolved by the Day 29 visit, based on laboratory results of low hemoglobin, absolute neutrophil count decreased, and platelet count decreased.
4. Incidence of Grade ≥ 3 infections, defined using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) (Section 10.3.5.1). Analysis methods are described in Section 10.3.5.

10.3.3. Secondary Endpoints

The secondary endpoints of the study are:

1. Type, frequency, and severity of all AEs and laboratory abnormalities (see Section 10.3.5)
2. Incidence of any Grade ≥ 3 AEs (see Section 10.3.5)
3. Median time to onset and median time to resolution of Grade ≥ 3 CRS and NT (see Section 10.3.5)
4. Use of tocilizumab and glucocorticoids for management of CRS and NT (see Section 10.3.5)
5. ORR (see Section 10.3.6.1)
6. CR rate (see Section 10.3.6.2)
7. DOR and duration of complete response (DoCR) following JCAR017 treatment (see Section 10.3.6.3)
8. Progression-free survival (PFS) and OS following JCAR017 treatment (see Section 10.3.6.4 and Section 10.3.6.5)
9. Maximum concentration (Cmax), time to peak concentration (Tmax), area under the curve (AUC), and other relevant PK parameters of JCAR017 in blood (see Section 10.3.7)
10. Measurement of HRQoL changes as assessed using the EORTC QLQ-C30 and the EuroQol instrument EQ-5D-5L (see Section 10.3.8)
11. Number of ICU inpatient days and non-ICU inpatient days and reasons for hospitalization (see Section 10.3.8)

12. Number of subjects transfused and the number of transfusions per subject (see Section 10.3.8)
13. Number of subjects requiring growth factor support (see Section 10.3.8)
14. Number of subjects requiring IVIG support (see Section 10.3.8)

10.3.4. Exploratory Endpoints

[redacted]

10.3.5. Safety Analysis

Safety analyses will be based on the JCAR017-treated Analysis Set. Safety analyses will be repeated using the Outpatient Analysis Set.

10.3.5.1. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs (TEAEs). A TEAE is defined as an AE that starts any time from initiation of JCAR017 administration through and including 90 days following JCAR017 administration. Any AE occurring after the initiation of another anticancer treatment will not be considered a TEAE. Adverse events of special interest will also be summarized.

For Grade ≥ 3 CRS and NT, time to onset is defined as the time from JCAR017 administration to the start date of the first occurrence. For these events, the time to resolution is defined as the time from the start date of the first occurrence to its resolution. In the absence of an event, subjects will be censored at the earliest of study completion, death, or the last date the subject was known to be alive on study. Kaplan-Meier methodology will be used to estimate the median time to onset and median time to resolution.

The number of subjects requiring tocilizumab and glucocorticoids for management of CRS and NT will be summarized descriptively.

Reporting of AEs will be based on MedDRA and CTCAE version 4.03, with the exception of CRS that will be graded according to the grading scale adapted from Lee (Lee 2014). TEAEs will be summarized by MedDRA SOC, preferred term (PT), and severity. A subject who reports multiple occurrence of TEAEs within the same SOC and PT is counted only once using the maximum severity grade for summaries.

10.3.5.2. Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology, serum chemistry) will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by at least 1 grade within 90 days after JCAR017 treatment. Any abnormality occurring after the initiation of another anticancer treatment will not be considered a treatment-emergent laboratory abnormality. The baseline value is defined as the last available recorded value on or prior to the date of the first dose of drug product.

If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Hematological and serum biochemistry data will be graded according to CTCAE Version 4.03, when applicable. Grade 0 includes all nonmissing values that do not meet the criteria for an abnormality of at least Grade 1. Grade 5 will not be used. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

Prolonged cytopenia is defined in Section 9.1.3 and is not based on the definition of treatment-emergent laboratory abnormalities. The frequency of subjects experiencing each individual laboratory abnormality and those with at least 1 abnormality on Day 29 will be summarized, as will recovery of prolonged cytopenia after Day 29.

10.3.5.3. Safety Subgroup Analysis

In the JCAR017-treated Analysis Set, safety subgroup analyses will be performed for baseline tumor burden (measured by the sum of product of the perpendicular diameters (SPD) or high serum LDH prior to the start of lymphodepletion), age, and CNS disease status. These as well as additional subgroup analyses, which may be performed, will be described in the SAP prior to database lock. Subgroup analyses will only be performed if there are at least 5 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.

10.3.5.4. Safety Monitoring Boundaries

Safety monitoring boundaries based on Bayesian framework (Thall 1994) have been included to help detect signals that may occur in the study. These boundaries are non-binding and the following toxicity events occurring within 30 days of a JCAR017 cell product infusion will be considered as safety events of interest for monitoring:

- A Grade 3 or above, JCAR017-related, treatment-emergent neurological toxicity
- Prolonged Grade 4 and Grade 5 individual safety events
  - Life-threatening (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
  - Death related to JCAR017 therapy

Whenever the safety boundaries are crossed, enrollment will be paused and an ad hoc SRC meeting will be held to review the data. The study will remain paused for enrollment pending the SRC recommendations. More information is available in the 017007 Statistical Analysis Plan (SAP).

10.3.6. Efficacy Analysis

Efficacy analyses will be based on the JCAR017-treated Analysis Set.

10.3.6.1. Objective Response Rate

The ORR analyses will be based on the JCAR017-treated Analysis Set, using Investigator assessments of disease status. The ORR is defined as the proportion of subjects with a best

overall response (BOR) of either a CR or PR. The BOR is the best disease response recorded from the time of the final JCAR017 infusion until disease progression, end of study, the start of another anticancer therapy, or HSCT. Best response will be assigned according to the following order: CR, PR, SD, PD, not evaluable, or not done.

10.3.6.2. Complete Response Rate

The complete response rate is defined as the proportion of subjects with a BOR of CR following JCAR017 treatment. The CR rate will be assessed as described for ORR above.

10.3.6.3. Duration of Response

Duration of response and DoCR following JCAR017 treatment are each defined as the time from first response to PD or death. If a subject does not have an event for the DOR or DoCR analysis, the subject will be censored at the date of the last adequate disease assessments on or prior to the earliest censoring event. The censoring reasons can include ongoing follow-up, discontinuation or completion of the study, receipt of another anticancer treatment, and subsequent transplant.

Kaplan-Meier methodology will be used to estimate DOR and DoCR.

10.3.6.4. Progression-free Survival

Progression-free survival is defined as the time from infusion of JCAR017 to progressive disease or death, whichever is earlier.

If a subject does not have an event for the PFS analysis, the subject will be censored at the date of the last adequate disease assessments on or prior to the earliest censoring event. The censoring reason can include ongoing follow-up, discontinuation or completion of the study, and receipt of another anticancer treatment.

Kaplan-Meier methodology will be used to estimate PFS.

10.3.6.5. Overall Survival

Overall survival is defined as the time from infusion of JCAR017 to the date of death. If a subject does not have an event for the OS analysis, the subject will be censored on the date the subject is last known to be alive.

Kaplan-Meier methodology will be used to estimate OS.

10.3.6.6. Efficacy Subgroup Analysis

In the JCAR017-treated Analysis Set, efficacy subgroup analyses may be performed on the same variables as specified in Section 10.3.5.3. Subgroup analyses will be performed for key safety summaries, and will only be performed if there are at least 5 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.

10.3.7. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed based on the PK Analysis Set.

The PK profile of JCAR017 cells in blood will be characterized, including Cmax, Tmax, AUC, and other relevant PK parameters. The kinetics of expansion of JCAR017 in the blood will be determined, along with the persistence of JCAR017 in the blood, based on the qPCR assay.

Pharmacokinetic parameters of qPCR-based JCAR017 transgene concentration in peripheral blood versus time will be displayed graphically, where possible.

Pharmacokinetic parameters will be estimated from the individual concentration-time profiles using a noncompartmental analysis approach.

Descriptive statistics for PK parameters will be categorized by efficacy and safety parameters and will include mean, standard deviation, coefficient of variation, minimum, and maximum. Median and ranges of values may be presented for selected variables.

Details of the pharmacokinetic analyses will be provided in the SAP or in a separate biomarker analysis plan.

10.3.8. Health-related Quality of Life and Health Economics and Outcomes Research

The analysis of HRQoL variables will include subjects who have baseline and at least 1 post-baseline value in the JCAR017-treated Analysis Set.

In the absence of a more specific hypothesis, the EORTC QLQ-C30 global health status score will be used as the primary HRQoL outcome with physical functioning and the fatigue symptom scale as secondary outcomes.

The EORTC QLQ-C30 and EQ-5D-5L will be analyzed according to the instrument-specific scoring manual. Scores for both instruments will be descriptively tabulated (number, mean, standard deviation, median, 95% confidence interval) at each timepoint. Single items will be also described in terms of number and frequency. Change from baseline in HRQoL outcomes will be summarized using descriptive statistics. Details will be given in the SAP.

Hospital resource utilization will be assessed based on the number of ICU and non-ICU inpatient days. The reasons for hospitalization, the number of subjects requiring packed red blood cell or platelet transfusions, the number of transfusions per subject, the number of subjects requiring growth factor support, and the number of subjects requiring IVIG support will be summarized. Descriptive statistics will be provided for subjects in the JCAR017-treated Analysis Set.

10.3.9. Nonconforming Product

If there are subjects who received at least 1 dose of nonconforming JCAR017 cell product, then subject disposition and baseline characteristics, safety and efficacy will be summarized separately for these subjects. Additional analyses for subjects receiving nonconforming product may be performed and will be described in the SAP prior to database lock.

10.4. Sample Size Considerations

Assuming a 30% drop out rate, a total of 114 subjects may be enrolled to ensure that approximately 80 subjects are treated with JCAR017, with a minimum of approximately 50 treated subjects monitored as an outpatient.

This study is designed for estimation and does not include formal hypothesis testing or adjustment for multiplicity. For any individual incidence rate (eg, AEs, ORR, CR), 80 subjects would provide a precision of ± 11.4% and 50 subjects would provide a precision of ± 14.5%, to estimate each endpoint assuming a confidence level of 95%. This is based on an event rate of 50% using the exact Clopper-Pearson method. Other rates would have narrower confidence intervals.

In Juno Study 017001, treatment with JCAR017 in subjects with R/R aggressive B-cell NHL resulted in observed incidence rates for Grade ≥ 3 CRS or NT, infections, and prolonged cytopenias of 12%, 9%, and 38%, respectively (data on file). If similar rates are observed in this study, this would provide sufficient precision for meaningful interpretation of the observed rates. Example rates and associated 95% confidence intervals are given in Table 8.

Table 8: Example Rates (± 95% Confidence Intervals)

Rate	Sample Size	Expected Count	Lower 95% CI	Upper 95% CI
50%	80	40	38.6%	61.4%
38%	80	30	26.9%	49.0%
12%	80	10	6.2%	21.8%
9%	80	7	3.6%	17.2%
50%	50	25	35.5%	64.5%
38%	50	19	24.6%	52.8%
12%	50	6	4.5%	24.3%
9%	50	4	2.2%	19.2%

Abbreviations: CI = confidence interval.

10.5. Timing of Analyses

Interim data may be analyzed and presented at scientific meetings.

An analysis is anticipated after at least 80 subjects have been treated with JCAR017 and these subjects have been followed for at least 6 months or until death, PD, or withdrawal from study.

Subjects treated with nonconforming product will not count towards the 80 subjects.

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 for this study.

11. DATA MANAGEMENT

11.1. Data Collection System

An electronic data capture (EDC) system provided by the Sponsor will be used for data collection. The EDC system is a fully validated, secure system that conforms to 21 CFR Part 11 requirements. Access to the EDC system is role-based, and login credentials will be provided only after completion of the assigned role-based training.

11.2. Data Quality

Study site personnel will enter data into the CRFs in the EDC system. The Sponsor Clinical Research Associate (CRA) or designee will verify data recorded in the CRFs with the source documents.

To ensure complete and accurate data, automated data validation checks programmed within the EDC system will flag missing and nonconformant data during data entry. Data review by the Sponsor project team may result in additional questions. Items flagged by the automated data validation checks and by the project team will appear as electronic queries on the applicable eCRF in the EDC system for a specified user role to resolve. All data entry and subsequent data changes are logged in an audit trail in the EDC system.

The Principal Investigator is responsible for ensuring that the data entered into the CRFs are complete and accurate and will electronically sign the CRFs for each subject prior to database lock.

Following database lock, an electronic copy of the final subject casebook will be provided to the study site for archival.

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Review

The study will be conducted in accordance with Good Clinical Practice (GCP), the protocol, and any other applicable Federal, state, and/or local regulatory requirements.

12.1.2. Institutional Review Board/Independent Ethics Committee Approval

It is the responsibility of the Investigator to ensure that the IRB has reviewed and approved this protocol prior to initiating the study. The IRB must also review and approve the investigative site's ICF, other written information provided to the subject, and all subject materials that may be used.

If the protocol, Investigator's Brochure, or ICF are amended during the study, per local regulations the Investigator is responsible for ensuring that the IRB has reviewed and approved these amended documents. In addition, IRB approval of the amended documents must be obtained before implementation and before new subjects are consented to participate in the study using the amended version of the ICF.

12.1.3. Institutional Biosafety Committee Approvals

JCAR017 consists of autologous T cells that have been manipulated via genetic modification in vitro to express a CAR directed against the CD19 cell surface marker. Since neither the subject source material nor the final drug product has been tested for the presence of communicable diseases in accordance with the provisions in 21 CFR §1271.90(a)(1), the JCAR017 drug product should be handled according to institutional procedures for materials that may contain infectious materials (eg, Biosafety Level 1 or 2).

It is the responsibility of the Investigator to ensure that the appropriate Institutional Biosafety Committee (IBC) has reviewed and approved this protocol, protocol amendments, and any other required materials prior to initiating the study if required per institutional policy.

Each site will be approved by the IBC in accordance with local procedures and country-specific regulatory requirements. Documentation of IBC approval must be in place prior to JCAR017 shipment to the site.

12.1.4. Subject Informed Consent

Prior to study entry, the Investigator, or a qualified person designated by the Investigator, will be responsible for explaining the nature, purpose, benefits, and risks of participation in the study to each subject, subject's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure). Sufficient time will be allowed to discuss any questions raised by the subject. The Investigator or designated staff will document this process in the study records. The Investigator must use the current IRB -approved consent form for documenting written informed consent. Each informed consent form will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and

also by an impartial witness if required by the IRB or local requirements. The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements (ICH E6) and local laws.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. The investigative site must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

12.2. Investigator Obligations

12.2.1. Investigator Responsibilities

The Investigator is responsible for ensuring that all study site personnel, including Sub-investigators and other responsible study staff members, conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents.

The Investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, 1998, and 21 CFR, Part 56, 1998.

The Investigator, Sub-Investigators, and key study staff as listed on FDA form 1572 will comply with 21 CFR, Part 54, 1998, providing documentation of any financial conflict of interest. This documentation must be provided prior to the Investigator's (and any Sub-Investigators) participation in the study. The Investigator and Sub-Investigator(s) agree to notify Juno Therapeutics of any change in reportable interests during the study and for 1 year following completion of the study at the Investigator's site. Study completion at a site is defined as the date when the study database is locked.

If necessary to amend either the protocol or the study ICF, the Investigator will be responsible for ensuring that the IRB reviews and approves the amended documents, and that subjects are informed of applicable changes, and updates.

The Investigator will sign and return to the Sponsor the "Protocol Signature Page" of the original protocol and any protocol amendment, provide current medical licenses, curriculum vitae, and the US FDA form 1572 "Statement of Investigator." All forms must be updated as applicable throughout the study.

12.2.2. Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB of progress of the study and notify the IRB of study closure. The Investigator must also provide the Sponsor with copies of all IRB correspondence that relate to study approvals, updates, or changes. The Investigator must also forward all IRB renewals to Juno Therapeutics.

12.3. Access to Information for Monitoring

Site monitoring is necessary to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct

of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). In accordance with regulations and guidelines, the designated the Sponsor CRA must have direct access to the Investigator's source documentation (including medical records, test and procedure results, investigator and study staff notes, etc.) in order to verify the accuracy of the data recorded in the eCRF.

The CRA is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The CRA should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the CRA to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

12.4. Site Audits and Regulatory Inspections

Representatives of regulatory authorities or the Sponsor may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Juno Therapeutics Study Manager immediately. The Investigator agrees to provide to representatives of a regulatory agency or Juno Therapeutics access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.5. Protocol Deviations

Protocol deviations must be sent to the IRB per their policies. The Investigator is responsible for knowing and adhering to the IRB requirements.

12.6. Quality Assurance and Quality Control

The Sponsor or its designee will perform quality control and quality assurance checks of all clinical studies that it sponsors. Before the enrollment of any subject in this study, the Sponsor personnel will review and provide training as needed to the Investigator, Sub-Investigators, and study site personnel regarding the following: protocol, IB, eCRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by the Sponsor CRAs or designees periodically throughout the study. During these visits, information recorded on the eCRFs will be verified against source documents, and requests for clarification or correction may be made. The eCRFs will be reviewed by the CRA for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. Requests for clarification or correction will be sent to Investigators via data queries.

12.7. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 and with requirements of the International Committee of Medical Journal Editors as a condition of consideration for publication of study results, Juno Therapeutics will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website per the US FDA requirement and that information at the website relating to study design and conduct is appropriately updated during the course of the study. Outside the US, this study and its results may be submitted for inclusion in appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

12.8. Study Completion

Upon completion or early termination of the study, the following activities, when applicable, must be conducted by the CRA and the Investigator:

- Return of all electronic and any nonelectronic study data to the Sponsor, if requested;
- Data clarifications and/or resolutions;
- Accounting, reconciliation, and final disposition of used and unused study drug; and
- Review of site study records for completeness.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason (see Section 4.5).

12.9. Site Termination

The Sponsor has the right to terminate a study site at any time for various reasons. Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Parts 312.50 and 312.56 and local regulations.

12.10. Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Records of subjects, source documents, monitoring visit logs, inventory logs of study drug product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. This includes any electronic records. These records will be retained in a secure file for the period required by the institution or site policy but not less than 25 years. Prior to the transfer or destruction of these records, Juno Therapeutics must be notified in writing and be given the opportunity to further store such records.

12.11. Confidentiality of Information

Individual subjects and their research data will be identified by a unique study identification number. Subjects' names will remain confidential and will not be included in the database. This confidentiality extends to testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

For tracking purposes and product chain of custody, subjects' name and name and date of birth will be communicated to the Sponsor's scheduling and manufacturing staff. This information will also be listed on the leukapheresis cell collection bag, and other containers throughout the JCAR017 manufacturing process. This information will be maintained in a separate limited-

access database and not together with any other clinical information. Only staff who need to use this information will have access to it.

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12.13. Publication Plan

Interim data from this study may be presented at scientific meetings. The Sponsor is responsible for the final clinical study report (CSR) prepared according to ICH guidelines. A final CSR will be prepared and will include any subject who has signed informed consent, regardless of whether the study is completed or prematurely terminated. If appropriate, an abbreviated or synoptic report may be prepared. The CSR will be in compliance with any applicable regulatory requirements and national laws and will be written in English.

12.14. Conflict of Interest

Any potential conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed in accordance with 21 CFR Part 54 (see Section 12.2.1).

13. CONTACT INFORMATION

13.1. Study Sponsor

Juno Therapeutics, Inc., a wholly-owned subsidiary of Celgene Corporation
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13.2. Global Drug Safety

Celgene Corporation: [redacted]

14. REFERENCES

Abramson JS, Palomba ML, Gordon LI, et al. Pivotal safety and efficacy results from TRANSCEND NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (R/R) large B-cell lymphomas. Blood 2019;134(suppl 1):241.

Abramson JS, Palomba ML, Gordon LI, et al. High durable CR rates in relapsed/refractory (r/r) aggressive B-NHL treated with the CD19-directed CAR T-cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort. Blood 2017;130(suppl 1): 581.

Actemra® [Prescribing Information]. South San Francisco, USA: Genentech Inc. [Internet];2013 [cited 21 Jan 2020] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125276s092lbl.pdf

Aoki R, Karube K, Sugita Y, et al. Distribution of malignant lymphoma in Japan: analysis of 2260 cases, 2001-2006. Pathol Int 2008;58(3):174-82

[redacted]

Brentjens RJ, Riviere I, Park JH, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. Blood 2011;118(18):4817-28.

[redacted]

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-68.

Couzin J, Kaiser J. Gene therapy. As Gelsinger case ends, gene therapy suffers another blow. Science 2005;307(5712):1028.

Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Front Immunol 2019;10:119.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130(16):1800-8.

Culpin RE, Sieniawski M, Angus B, et al. Prognostic significance of immunohistochemistry-based markers and algorithms in immunochemotherapy-treated diffuse large B-cell lymphoma patients. Histopathology 2013;63(6):788-801.

Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet 2013;381(9880):1817-26.

Czuczman MS, Davies A, Linton KM, et al. A phase 2/3 multicenter, randomized study comparing the efficacy and safety of lenalidomide versus investigator's choice in relapsed/refractory DLBCL. Blood 2014; 124:628.

Davila ML, Brentjens R, Wang X, et al. How do CARs work? Early insights from recent clinical studies targeting CD19. Oncoimmunology 2012;1(9):1577-83.

Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6(224):224-5.

Donahue RE, Kessler SW, Bodine D, et al. Helper virus induced T cell lymphoma in nonhuman primates after retroviral mediated gene transfer. J Exp Med 1992;176(4):1125-35.

El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Ann Oncol 2007;18(8):1363-68.

FDA. Supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors [Internet];.2006 [cited 21 Jan 2020]. Available from: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/supplemental-guidance-testing-replication-competent-retrovirus-retroviral-vector-based-gene-therapy.pdf.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. [Internet];2013 [cited 29 June 2017]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.

[redacted]

Friedberg JEW. Double-hit diffuse large B-cell lymphoma. J Clin Oncol 2012;30(28):3439-43.

Fu K, Weisenburger DD, Choi WWL, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell–like and non–germinal center B-cell–like subtypes of diffuse large B-cell lymphoma. J Clin Oncol 2008;26(28):4587-94.

[redacted]

Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med 2013;368(16):1509-1518.

[redacted]

Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 2003;302(5644):415-9.

[redacted]

Issa DE, van de Schans SA, Chamuleau ME, et al. Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010. Haematologica 2015;100(4):525-33

Jacobsen E, Pozdnyakova O, Redd R, et al. Imatinib mesylate lacks efficacy in relapsed/refractory peripheral T cell lymphoma. Leuk Lymphoma 2015;56(4):993-8.

[redacted]

Kochenderfer JN, Dudley ME, Kassim S, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33(6):540-9.

Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385(9967):517-28.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25(4):625-38.

[redacted]

Li YS, Hayakawa K, Hardy RR. The regulated expression of B lineage associated genes during B cell differentiation in bone marrow and fetal liver. J Exp Med 1993;178(3):951-60.

Li YS, Wasserman R, Hayakawa K, et al. Identification of the earliest B lineage stage in mouse bone marrow. Immunity 1996;5(6):527-35.

Li Z, Dullmann J, Schiedlmeier B, et al. Murine leukemia induced by retroviral gene marking. Science 2002;296(5567):497.

[redacted]

Maloney D, Abramson J, Palomba ML, et al. Safety profile of the CD19-directed defined composition CAR T-cell product JCAR017 (lisocabtagene maraleucel; liso-cel) in relapsed/refractory aggressive B-NHL patients: potential for outpatient administration. Blood 2017; 130(suppl 1);1552.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371(16):1507-17.

McGarrity GJ, Hoyah G, Winemiller A, et al. Patient monitoring and follow-up in lentiviral clinical trials. J Gene Med 2013;15:78-82.

Modlich U, Kustikova OS, Schmidt M, et al. Leukemias following retroviral transfer of multidrug resistance 1 (MDR1) are driven by combinatorial insertional mutagenesis. Blood 2005;105(11):4235-46.

Morgan RA, Chinnasamy N, Abate-Daga D, et al. Cancer regression and neurological toxicity following anti-MAGE-A3 TCR gene therapy. J Immunother 2013;36(2):133-51.

Mounier N, El Gnaoui T, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. Haematologica 2013;98(11):1726-31.

Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. Am J Hematol 2013;88(10):890-94.

NCCN. National comprehensive cancer network clinical practice guidelines in oncology. (NCCN Guidelines®): B-cell lymphomas. Version 3 [Internet];2019 [cited 21 Jan 2020]. Available from: http://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician gls/pdf/b-cell.pdf.

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377(26):2531-44.

[redacted]

Novelli S, Briones J, Sierra J. Epidemiology of lymphoid malignancies: last decade update. Springerplus 2013;2(1):70.

[redacted]

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality of life scores. J Clin Oncol 1998; 16 (1): 139-44.

[redacted]

Pettengell R, Coiffier B, Narayanan G, et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. Lancet Oncol 2012;13(7):696-706.

Porter DL, Levine BL, Bunin N, et al. A phase 1 trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation. Blood 2006;107(4):1325-31.

[redacted]

Rigacci L, Puccini B, Cortelazzo S, et al. Bendamustine with or without rituximab for the treatment of heavily pretreated non-Hodgkin's lymphoma patients: A multicenter retrospective study on behalf of the Italian Lymphoma Foundation (FIL). Ann Hematol 2012;91(7):1013-22.

RoActemra® [Summary of Product Characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited [Internet];2018 [cited 21 Jan 2020]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR Product_Information/human/000955/WC500054890.pdf.

Rothe M, Modlich U, Schambach A. Biosafety challenges for use of lentiviral vectors in gene therapy. Curr Gene Ther 2013;13(6):453-68.

Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Canc Discov 2013;3(4):388-98.

Scholler J, Brady TL, Binder-Scholl G, et al. Decade-long safety and function of retroviral modified chimeric antigen receptor T cells. Sci Transl Med 2012;4(132):132ra153.

Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome and potential for cytokine- directed therapies. Annu Rev Med 2015;66:145-159.

Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of juliet: A global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Blood 2017;130(suppl 1);577.

SEER. Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Factsheets: Non-Hodgkin Lymphoma.[Internet];2019 [cited 21 Jan 2020] Available from: https://seer.cancer.gov/statfacts/html/nhl.html.

[redacted]

Siegel RL, Miller KD, Jemal A. Cancer statistics 2019. CA Cancer J Clin 2019;69(1):7-34.

Smith A, Crouch S, Lax S, et al. Lymphoma incidence, survival and prevalence 2004-2014: sub-type analyses from the UK's haematological malignancy research network. Br J Cancer 2015;112(9):1575-84.

Stamenkovic I, Seed B. CD19, the earliest differentiation antigen of the B-cell lineage, bears three extracellular immunoglobulin-like domains and an epstein-barr virus-related cytoplasmic tail. J Exp Med 1988;168(3):1205-10.

Thall PF, Simon R. Practical bayesian guidelines for phase IIB clinical trials. Biometrics 1994;50(2):337-349

Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016;126(6):2123-38.

Turtle C, Hanafi L, Berger C, et al. High rates of durable complete response in ALL, NHL and CLL after immunotherapy with optimized lymphodepletion and defined composition CD19 CAR-T cells (JCAR014). J Clin Oncol 2016;34(suppl 15);102.

Turtle CJ, Maloney DG. Clinical trials of CD19-targeted CAR-modified T-cell therapy; a complex and varied landscape. Exp Rev Hematol 2016a:1-3.

Turtle CJ, Riddell SR, Maloney DG. CD19-targeted chimeric antigen receptor-modified T cell immunotherapy for B cell malignancies. Clin Pharmacol Ther. 2016b Sep;100(3):252-8.

Vacirca JL, Acs PI, Tabbara IA, et al. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2013;93(3):403-9.

Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant 2016;51(1):51-7.

Wang GP, Levine BL, Binder GK, et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Mol Ther 2009;17(5):844-50.

Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27(9):1902-9.

Yescarta®.[Prescribing Information]. Santa Monica, USA: Kite Pharma, Inc.; 2019. Available from: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf

Ziepert M, Hasenclever D, Kuhnt E, et al. Standard international prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28(14):2373-80.

APPENDIX A. SCHEDULES OF EVALUATIONS

STUDY 017007: SCREENING ASSESSMENTS	
Obtain Consent	x
Inclusion/Exclusion Criteria (5)	x
Medical History	x
ECOG	x
Physical Examination (8.3.2)	x
12-lead ECG	x
MUGA/ECHO	x
Viral Serology (8.3.7)	x
Serum Pregnancy (8.3.7)	x
PET Scans(8.3.1)	x[a]
CBC with Differential (8.3.7)	x
Chemistries (8.3.7)	x
Pathology Report[b]	x
Record all AEs/SAEs related to study procedures and concomitant medications taken at that time	x

Note: If a subject has had a screening procedure as standard of care within 30 days of consent, it may be used to evaluate study eligibility after discussion with the Sponsor.
AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; MUGA = multiple uptake gated acquisition scan; PET = positron emission tomography; SAE = serious adverse event.

[a] PET scan may be performed more than 30 days prior to screening if no intervening anticancer treatments have been performed.

[b] For subjects with tDLBCL, a pathology report from the biopsy of their current relapsed disease is required.

STUDY 017007: LEUKAPHERESIS ASSESSMENTS	
CBC w/differential (8.3.7) on the day of (or within 24 hours prior to) leukapheresis. CBC must include ALC	x
Vital Signs (8.3.3), before and after leukapheresis	x
Leukapheresis (3)	x
Record all AEs/SAEs related to study procedures and concomitant medications taken at that time	x

AE = adverse event; ALC = absolute lymphocyte count; CBC = complete blood count; SAE = serious adverse event.

STUDY 017007: PRETREATMENT, TREATMENT, AND POST-TREATMENT ASSESSMENTS																		
	Screening	**Pre-treatment Period**	**Treatment Period**								**Post-treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment**							
Study Day	**Approxi-mately 1-2 Weeks Prior to Leuka-pheresis**	**Within 7 days Prior to Lympho-depletion**	**Lympho-depletion Ending Day -7 to 2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**18**	**N/A**	**24**
Visit Window (days)					**± 1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**N/A**	**± 14**
Procedure (protocol section)																		
Informed consent	x																	
I/E criteria (5)	x	x		x														
Medical history	x																	
Pathology report*	x																	
ECOG (8.3.8)	x	x	x	x														
Height/weight		x		x[h]														
Physical examination (8.3.2)	x	x		x	x[j]	x	x[j]	x	x	x	x[b]	x[b]	x[b]	x[b]	x	x[b]		x
Routine neurological examination (8.3.3)	x	x		x	x	x	x	x	x	x	x[b]	x[b]	x[b]	x[b]	x	x[b]		x
MMSE (8.3.3)		x		x[v]	x[v]	x[v]	x[v]	x[v]	x[v]	x[v]	x[v]	x[b,v]	x[b,v]					
Vital signs (8.3.4)		x	x[g]	x[i]	x	x	x	x	x	x								
Diary of daily temperature recording				(Subject to monitor temperature at home 3x/day and anytime they feel feverish or have chills)														
MUGA/ECHO (8.3.9)	x	x**																

STUDY 017007: PRETREATMENT, TREATMENT, AND POST-TREATMENT ASSESSMENTS																		
	Screening	**Pre-treatment Period**	**Treatment Period**								**Post-treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment**							
Study Day	**Approxi-mately 1-2 Weeks Prior to Leuka-pheresis**	**Within 7 days Prior to Lympho-depletion**	**Lympho-depletion Ending Day -7 to 2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**18**	**N/A**	**24**
Visit Window (days)					**± 1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**N/A**	**± 14**
12-lead ECG(8.3.10)	x	x																
HRQoL questionnaires (8.3.13.1)		x		x						x	x	x	x	x	x	x	x	x
Serum pregnancy test (8.3.7)	x	x[a]										x	x	x	x			
Lymphodepleting chemo (8.2.5)			x[g]															
JCAR017 administration (8.2.5.3)				x[u]														
Tumor biopsy (8.3.5)	x[k]																x	
CT (8.3.1)		x[c]								x[l]		x[m]	x[m]	x[m]	x[m]	x[m]		x[m]
PET (8.3.1)	x	x[c]								x[l]		x[m,n]	x[m,n]	x[m,n]	x[m,n]	x[m,n]	x	x[m,n]
MRI of brain (8.3.1)		x[e]								x[d]		x[d]	x[d]	x[d]	x[d]	x[d]		x[d]
CBC w/differential (8.3.7)	x	x		x	x	x	x	x	x	x	x[b]	x[b]	x[b]	x[b]	x[b]	x[b]		x
Coagulation (8.3.7)		x		x	x	x	x	x	x	x								x
Chemistries (8.3.7)	x	x	x	x	x	x	x	x	x	x								x
Inflammatory markers (8.3.7)		x		x	x	x	x	x	x[d]	x[d]								
Serum immunoglobulins (8.3.7)		x								x	x[s]	x[s]	x[s]	x[s]	x[s]	x[s]		x[s]

STUDY 017007: PRETREATMENT, TREATMENT, AND POST-TREATMENT ASSESSMENTS																		
	Screening	**Pre-treatment Period**	**Treatment Period**								**Post-treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment**							
Study Day	**Approxi-mately 1-2 Weeks Prior to Leuka-pheresis**	**Within 7 days Prior to Lympho-depletion**	**Lympho-depletion Ending Day -7 to 2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**18**	**N/A**	**24**
Visit Window (days)					**± 1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**N/A**	**± 14**
Peripheral blood for PK by qPCR (8.3.12.1)		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral blood sample for viral vector sequence by qPCR (8.3.12.2)		x		x		x	x	x	x	x	x	x	x	x	x	x[o]	x[o]	x[o]
[redacted] and Immunogenicity Assessments (Section 8.3.12.5)		x[x]		x	x	x	x	x[x]	x	x[x]	x[x]	x[x]	x[x]	x[x]	x[x]	x	x[x]	x
Peripheral blood sample for RCL testing (8.3.12.6)		x										x	x		x			x[t]
CSF assessment (8.3.11)		x[e]								x[e]		x[e]	x[e]	x[e]	x[e]	x[e]		x[e]
BMB/BMA (8.2.8)				As clinically indicated														

STUDY 017007: PRETREATMENT, TREATMENT, AND POST-TREATMENT ASSESSMENTS																		
	Screening	**Pre-treatment Period**	**Treatment Period**								**Post-treatment (Follow-Up, Disease Progression, EOS) Note: efficacy evaluations (CT, PET) not required after PD or subsequent anticancer treatment**							
Study Day	**Approxi-mately 1-2 Weeks Prior to Leuka-pheresis**	**Within 7 days Prior to Lympho-depletion**	**Lympho-depletion Ending Day -7 to 2[f]**	**1[f]**	**4**	**8**	**11**	**15**	**22**	**29**	**60**	**90**	**180**	**270**	**365**	**545**	**PD**	**730 (EOS)**
Month	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**2**	**3**	**6**	**9**	**12**	**18**	**N/A**	**24**
Visit Window (days)					**± 1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**± 14**	**N/A**	**± 14**
AEs/SAEs (9)	AEs/SAEs related to protocol-mandated procedure		Collect all AEs from lymphodepleting chemo to 90 days post-last dose of JCAR017[p]										AEs/SAEs related to JCAR017 and/or protocol-mandated procedures[q,r,] as well as selected AEs listed in section 9					
Concomitant medications (6.5)		Con meds associated with AEs/SAEs related to protocol-mandated procedures	Collect all concomitant meds from lymphodepleting chemo to 90 days after the last dose of JCAR017										Concomitant meds ongoing at the time of AEs/SAEs related to JCAR017 and/or protocol-mandated procedures, corticosteroids, GVHD meds, and anticancer therapies					
Anticancer therapies			Throughout study															
Hospitalizations (8.3.14)			From first day of lymphodepleting chemotherapy to end of study															

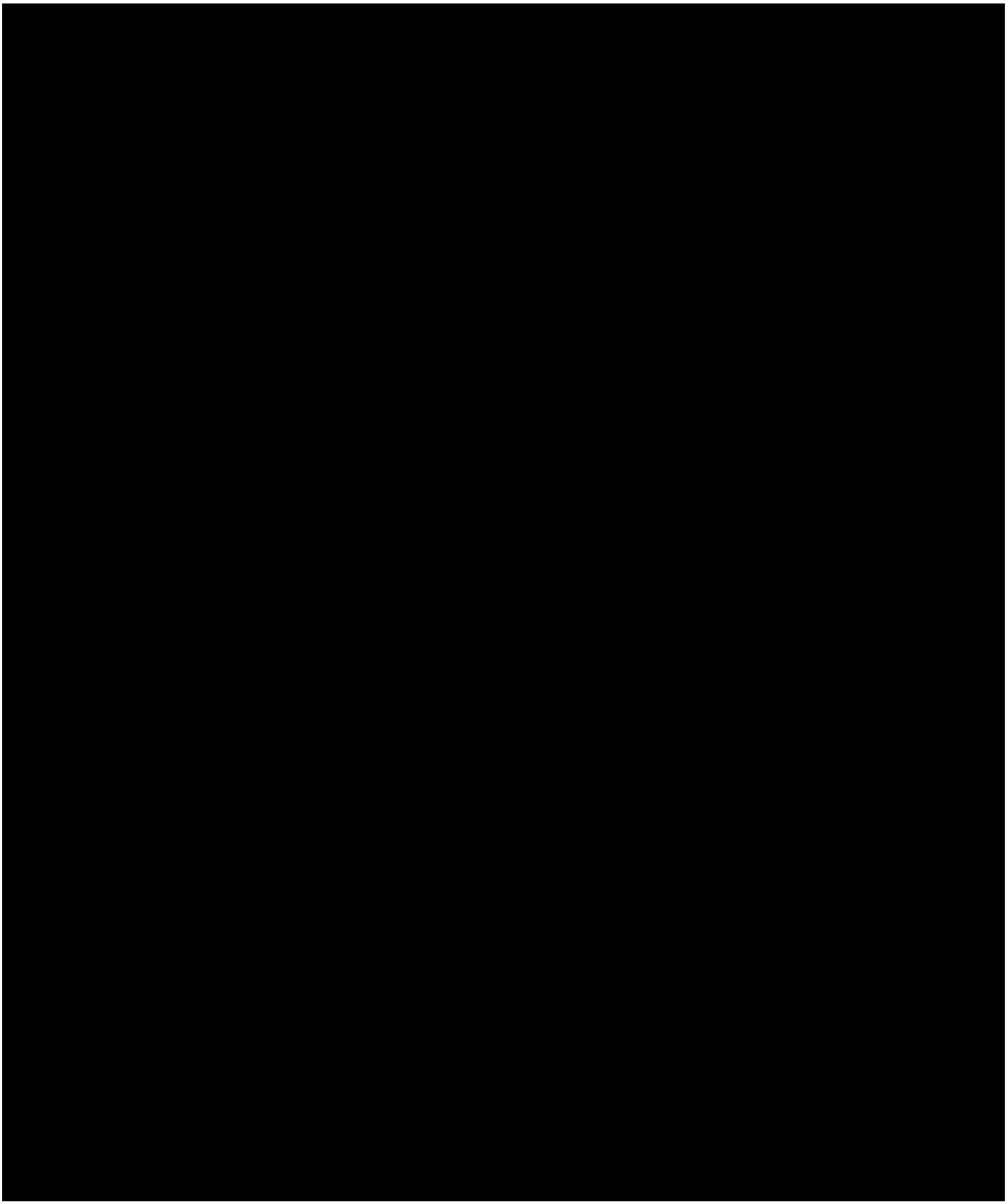
AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; CSF = cerebrospinal fluid; CT = computed tomography; EOS = end of study; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GVHD = graft-versus-host disease; HRQoL = health-related quality of life; I/E = inclusion/exclusion; MMSE = Mini-Mental State Exam; MRI = magnetic resonance imaging; MUGA = multiple uptake gated acquisition scan; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; qPCR = quantitative polymerase chain reaction; RCL = replication-competent lentivirus; SAE = serious adverse event.

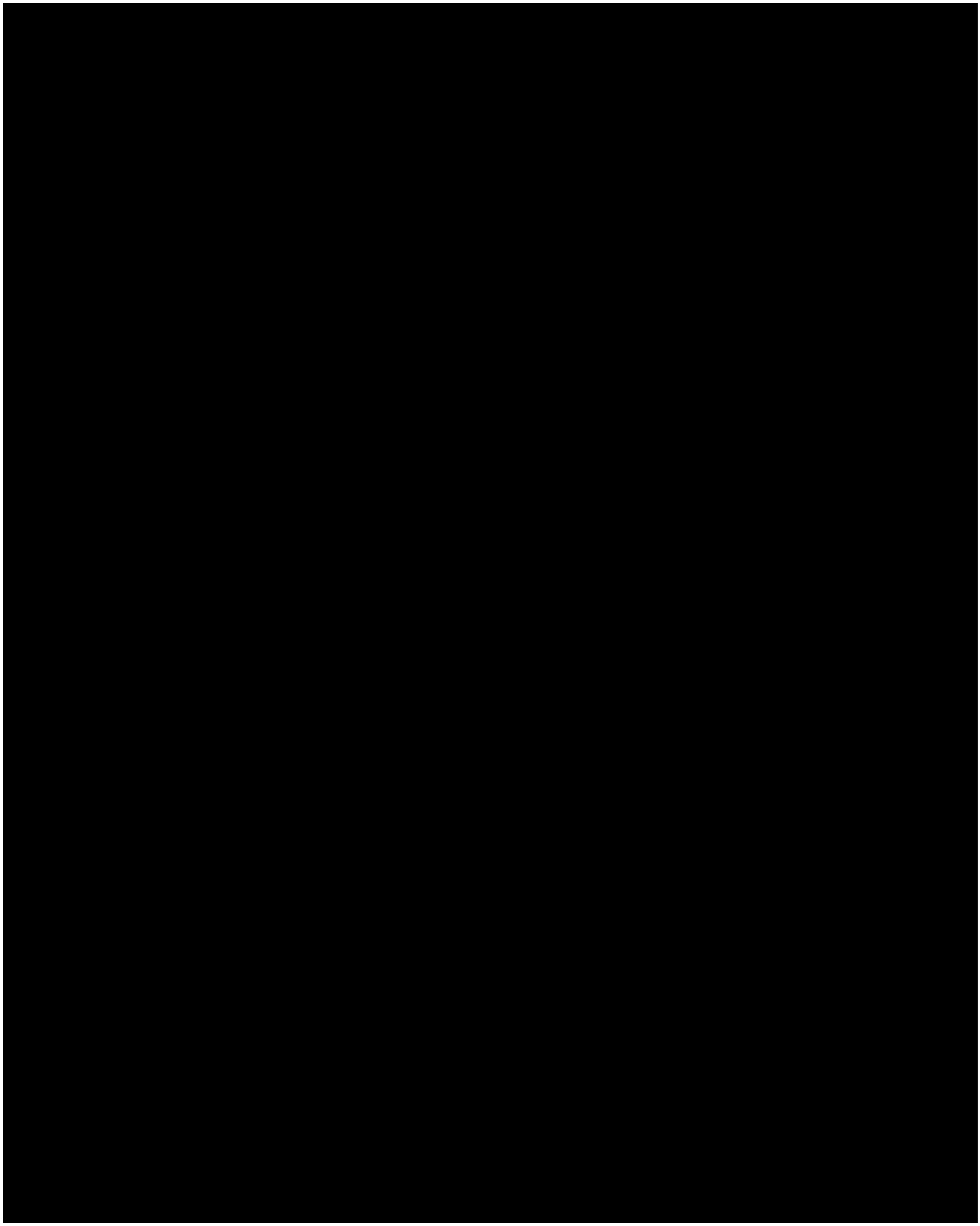
Schedule of Evaluations Footnotes:

a) Serum pregnancy test must be done within 48 hours prior to lymphodepleting chemotherapy.
b) Not done for subjects who have received subsequent anticancer therapy.
c) Not required if done at the study site for screening and no intervening antitumor therapy has been administered. If required, recommended within 14 days prior to the start of lymphodepleting chemotherapy and must be done within 6 weeks prior to the start of lymphodepleting chemotherapy. For subjects that receive anticancer treatment for disease control while JCAR017 is being produced, these assessments must be performed after completion of the intervening anticancer treatment and as close as possible to the start of lymphodepleting chemotherapy (recommended within 7-14 days prior to start).
d) If clinically indicated.
e) Required only for subjects with suspected or confirmed CNS involvement, or as clinically indicated.
f) All evaluations and laboratory assessments must be done prior to administration of lymphodepleting chemotherapy or JCAR017.
g) To be done on each day of lymphodepleting chemotherapy. Prior to first dose, it must be confirmed that the subject meets criteria for lymphodepleting chemotherapy as described in Section 8.2.5.2.
h) Weight only.
i) Measured within approximately 5 minutes before and 15 minutes after infusion, then approximately every 15 minutes thereafter for the first hour and hourly (±15 minutes) for the next 2 hours. Continue to monitor vital signs after this point until stable and as clinically indicated.
j) Routine neurological examination only.
k)For subjects with tDLBCL, a pathology report from the biopsy of their current relapsed disease is required.
l) PET and CT scan may be performed Day 22 to Day 29.
m) If CR is achieved, only CT scans will be required. Upon progression/relapse or initiation of another anticancer treatment, PET and CT scans are no longer required. Subjects who receive HSCT post-JCAR017 but no other anticancer treatment should continue to undergo PET and/or CT scans in accordance with the previous 2 sentences. PET scans should be performed to verify PD.

** MUGA/ECHO must be repeated after any intervening cardiotoxic anticancer therapy.

n) Not required if CR previously documented.
o) If more than 1% of cells in test samples collected at the Day 365 visit or later test positive for vector sequences, the pattern of vector integration sites will be analyzed. If a predominant integration site is detected, then the subject will be asked to provide another blood sample 3 months later for follow-up testing.
p) If a subject receives lymphodepleting therapy but not JCAR017, all AEs/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy. For subjects starting a subsequent nonchemotherapy-containing anticancer therapy (eg, checkpoint inhibitors, IMIDs) prior to 90 days following final JCAR017 administration, all AE/SAEs will be collected after initiation of the subsequent therapy for 90 days following final JCAR017 infusion or 30 days following subsequent therapy, whichever is longer. For subjects starting a subsequent chemotherapy-containing anticancer therapy prior to 90 days following final JCAR017 administration, only AEs and SAEs related to JCAR017 and/or protocol-mandated procedures must be recorded/reported after initiation of subsequent therapy.
q) Starting from 91 days after the last dose of JCAR017 until EOS visit.
r) If any of the following clinical conditions are observed, an SAE should be reported unless the event can be definitely attributed to an alternative cause: new/secondary malignancies; new onset or exacerbation of a pre-existing neurologic disorder; new onset of a rheumatologic or other autoimmune disorder; new onset of a hematologic disorder; rare and unexpected disorders with an unknown etiology (eg, Guillain-Barré, Stevens-Johnson syndrome).
s) Not required if B-cell recovery documented without recent administration of intravenous immune globulin.
t) Samples may be archived if all samples collected within the first year after the last dose of JCAR017 were tested and were negative for RCL.
u) Prior to dose, it must be confirmed that the subject meets criteria for JCAR017 treatment as described in Section 8.2.5.3.
v) Not required if the subject is medically incapacitated and/or medically unable to complete.
w) Pregnancy test and contraceptive counseling for women of childbearing potential.
x) Immunogenicity Assessment; samples will be processed to plasma and analyzed for the presence of antibodies that bind to the extracellular region of JCAR017.





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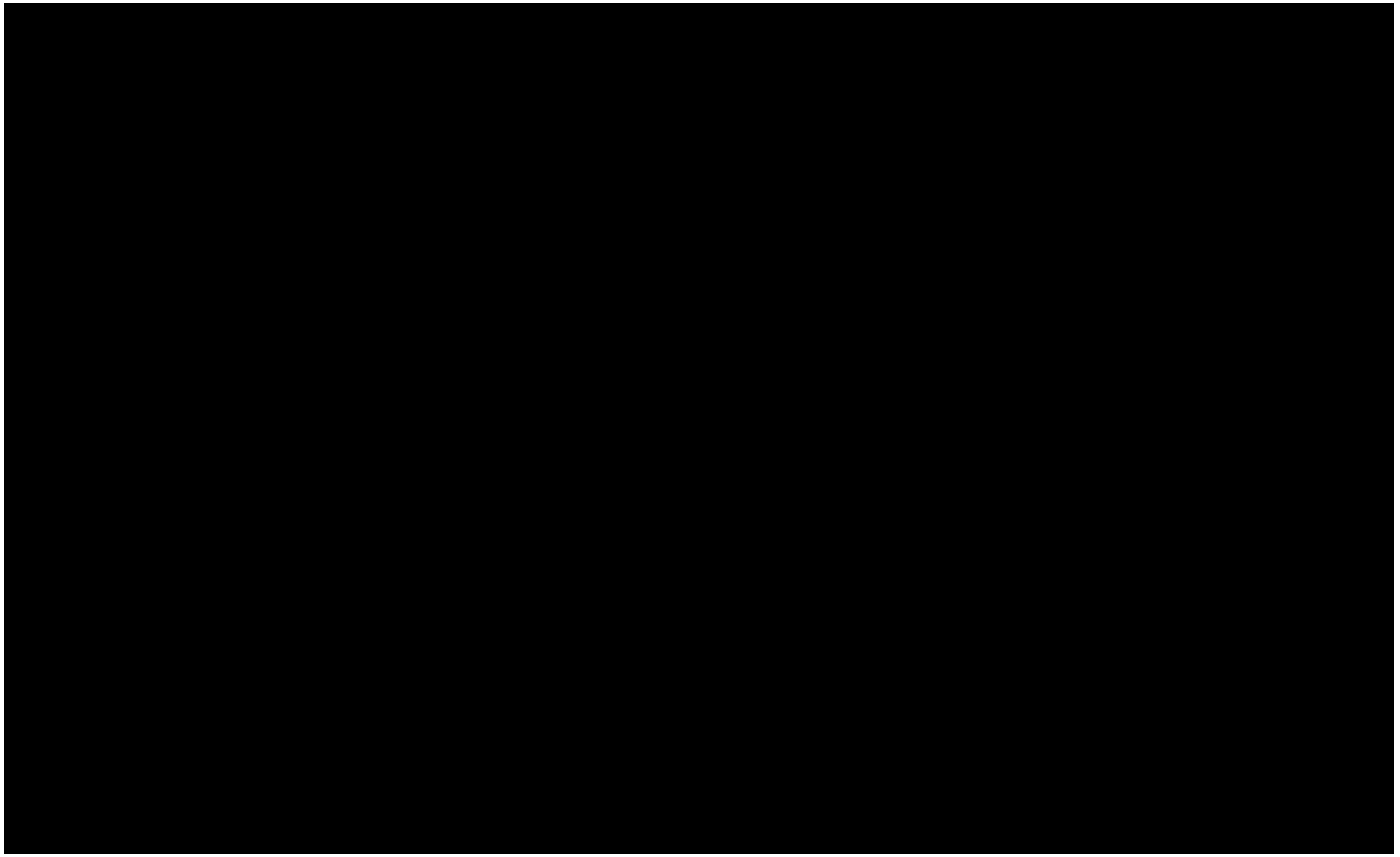

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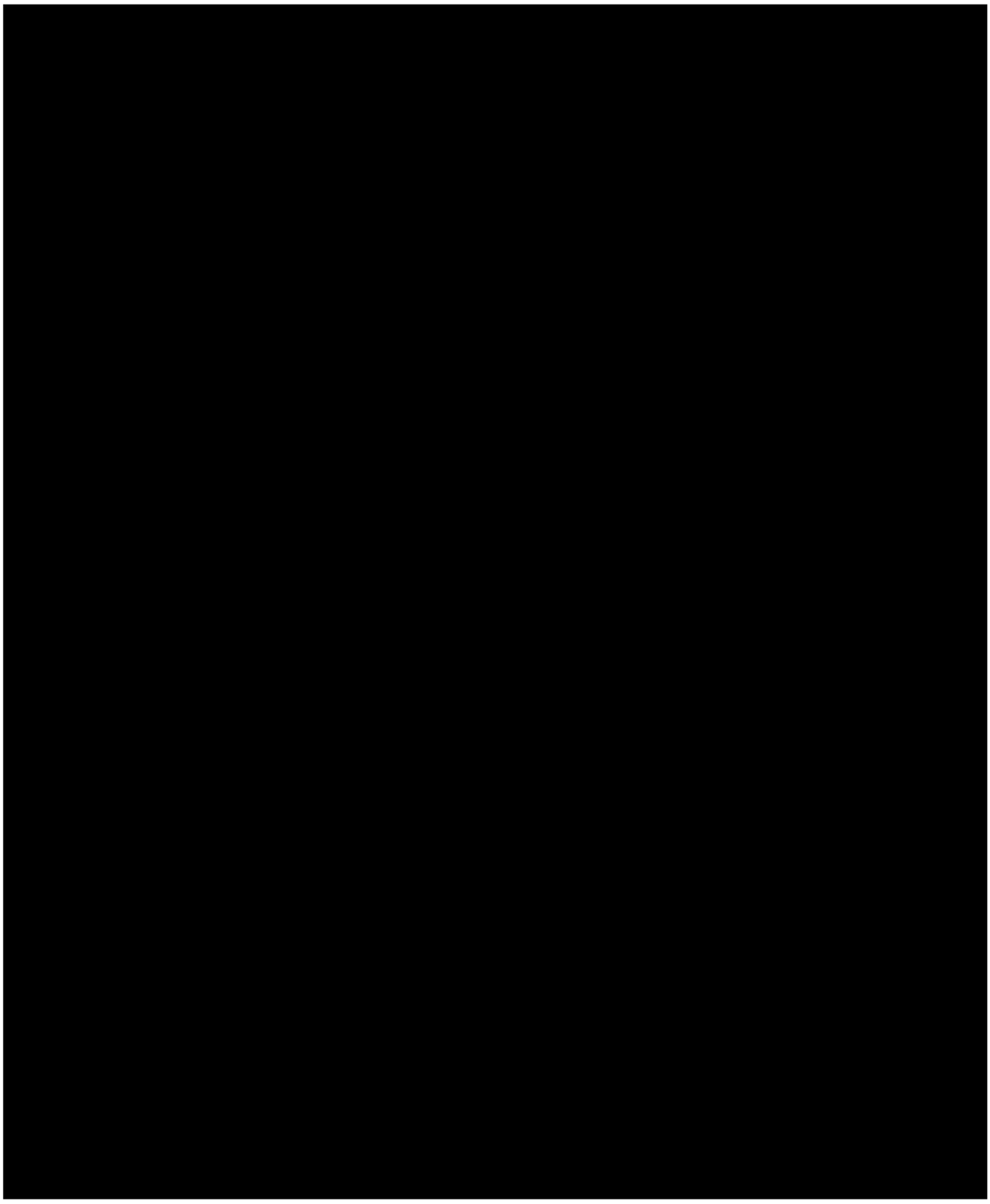

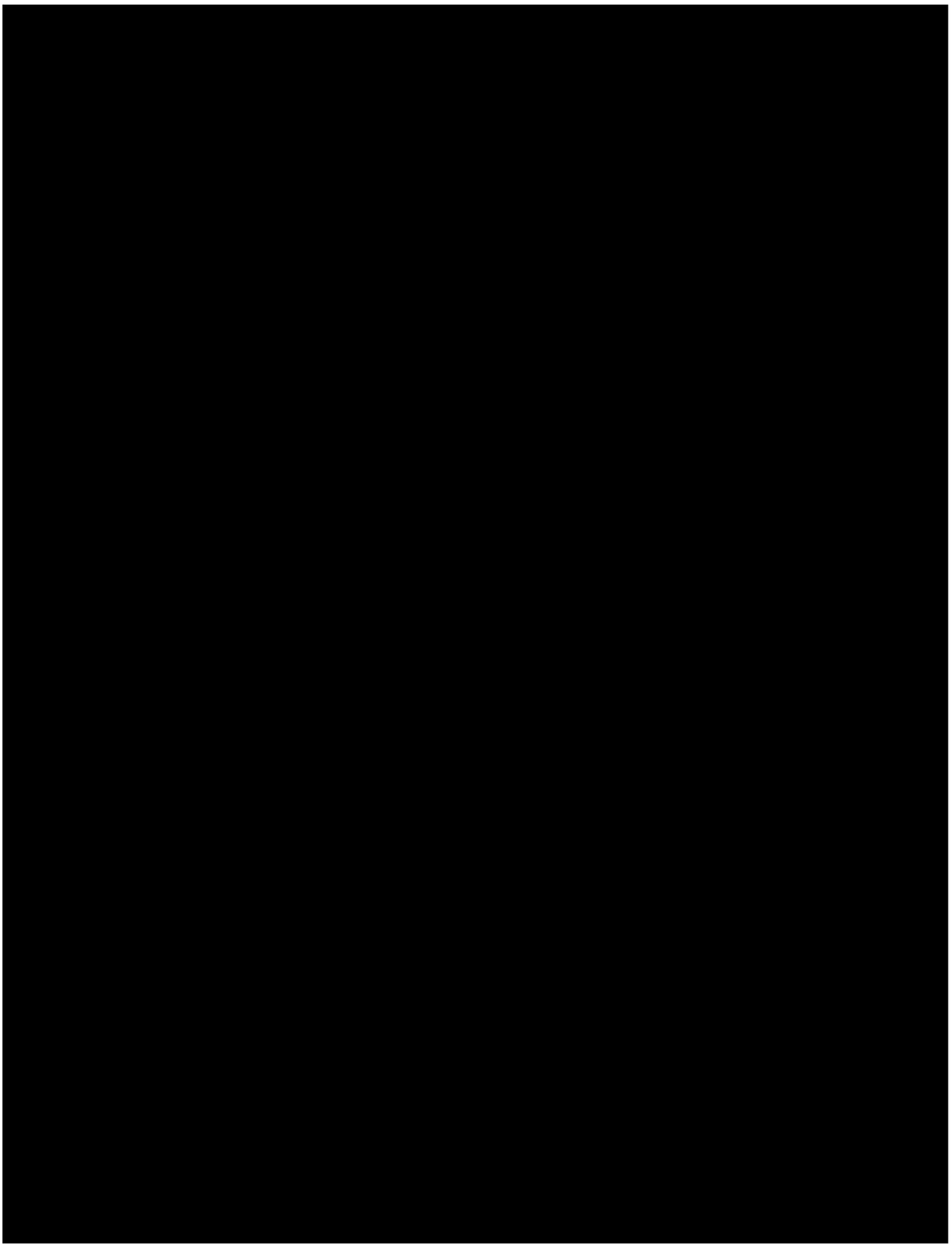

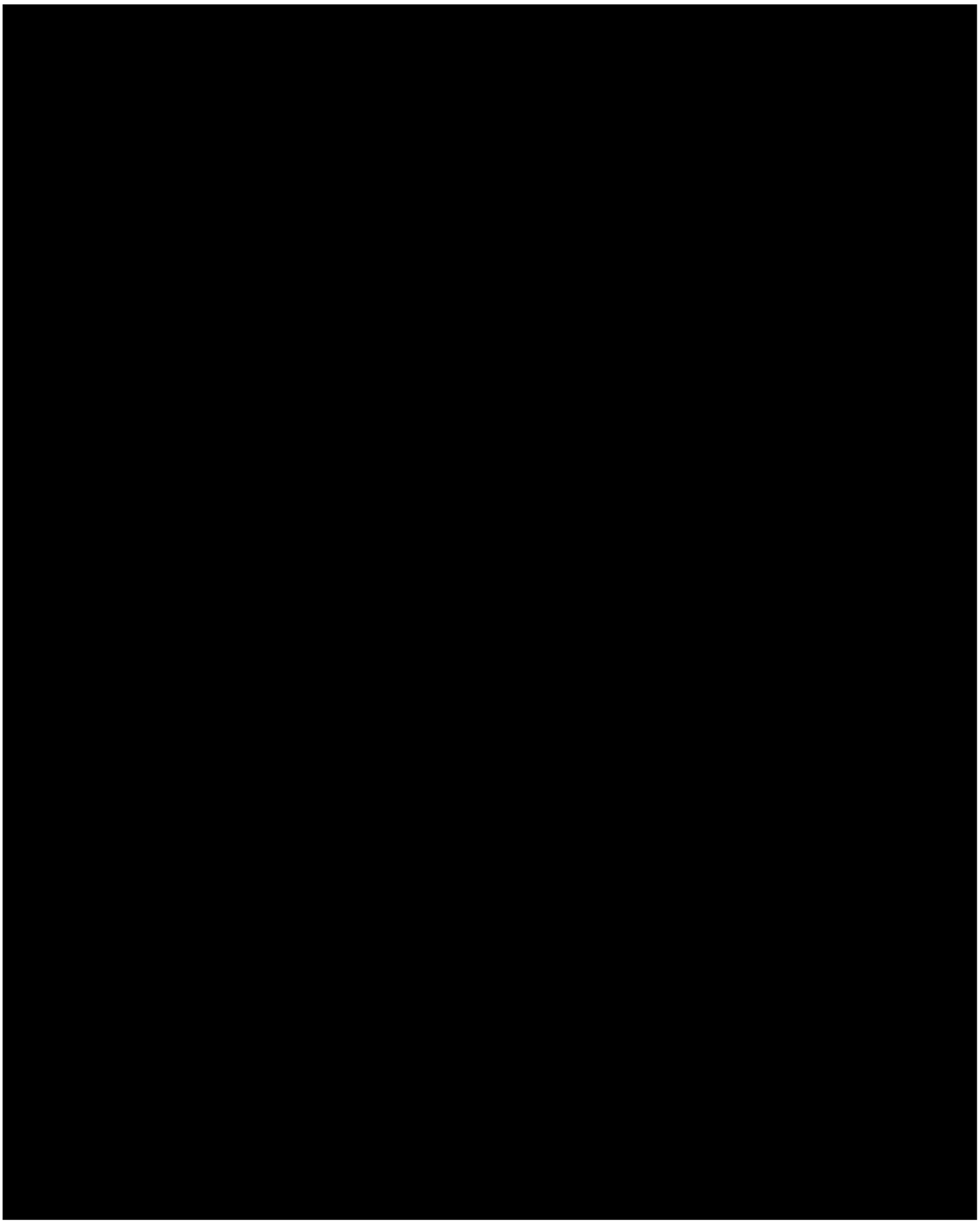

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Monday, 23 March 2020, 09:29 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Study Population

- **Revised exclusion criteria regarding tumor invasion of vessels and deep venous thrombosis (DVT)/pulmonary embolism (PE)** [redacted] Thus, the exclusion criteria have been revised to only exclude patients with venous thrombosis or embolism not managed on a stable regimen of anticoagulation or patients with progressive vascular tumor invasion, thrombosis, or embolism.

  Revised Sections: Protocol Synopsis, Section 5.2 Exclusion Criteria, Section 8.2.5.3 Criteria for JCAR017 Treatment

The amendment also includes several other minor updates, clarifications and corrections:

- Protocol title page updated study acronym from TRANSCEND-OUTREACH to TRANSCEND-OUTREACH-007
- Protocol title page updated to include Study ID, NCT number, and 017007 Medical Monitor mailbox email
- Added more detail regarding safety analyses, including more detail on adverse events of special interest (AESIs) to be analyzed (Protocol Synopsis, Section 2.4, Section 9.1.3)
- Estimated total time for all subjects to complete the study from 4 years to approximately 5 years (Protocol Synopsis, Section 4.2)
- Clarified exclusion criteria of active hepatitis B and hepatitis C (Protocol Synopsis, Section 5.2)
- Updated contraception requirements, lactation, and pregnancy language (previously described in Section 5.3) and in Inclusion Criteria to align with program-wide changes. Pregnancy tests and contraceptive counseling for females of childbearing potential were also added at study visits every 3 months until 12 months after lymphodepleting chemotherapy (LDC) (Protocol Synopsis, Section 5.1, Section 9.3.6, Appendix A)

- Updated total dose of JCAR017 from $1x10^8$ to $100x10^6$ CAR+ T cells (Protocol Synopsis, Section 6)
- Updated information on approved CAR-T cells and clinical experience with JCAR017 (Section 1.3, Section 1.4, Section 1.5)
- Added death as a possible reason for subject discontinuation prior to receiving study treatment (Section 5.3.2)
- Updated nonconforming product language, including reference to the Protocol Product Deviation Plan and clarified exceptions for use (Section 6.3.1, Section 6.3.2)
- Updated JCAR017 preparation and administration section to include the option of an on-site liquid nitrogen (LN2) freezer for storage (Section 6.3.7)

[redacted]

- Clarified language in the prohibited concomitant medications section (Section 6.6)

[redacted]

- Added guidance that, if available and adopted as per site standard practice, cytokine release syndrome (CRS) and neurotoxicity (NT) grading according to the American Society of Bone Marrow Transplantation (ASTCT) Consensus Grading System should also be recorded in the electronic case report form (eCRF) to inform future modifications of the management guidelines (Section 7.1)
- Added new language regarding Second Primary Malignancies Follow-up Period to align with JCAR017 program protocols (Section 7.12, Section 8.2.11)
- Added that tocilizumab is not indicated for treatment of neurologic toxicities (Section 7.3)
- Clarified positron emission tomography (PET) scan requirement at screening to remove language allowing Investigator confirming continued disease presence without a PET (Section 8.2.1)
- Clarified circumstances under which PET scan may be performed longer than 30 days prior to screening (Section 8.2.1, Appendix A Schedules of Evaluations)
- Added clarification on biomarker collection for immunogenicity testing (Section 8.2.4, 8.3.12, 8.3.12.5, Table 1 Study Objectives and Endpoints, Appendix A Schedules of Evaluations)
- Prior to LDC, clarified that subjects should not experience a significant worsening in clinical status compared to the initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with LDC or exclude them from treatment with JCAR017 (Section 8.2.5.1)

- Clarified that creatinine clearance is required only on the first date of LDC (Section 8.2.5.2)
- Updated safety reporting requirements to align with program-wide updates (Section 9)
- Added new language regarding Future Use of Stored Specimens and Data (Section 12.12)
- References were updated (Section 14)
- Added quality of life questionnaire requirement at disease progression timepoint (Appendix A Schedules of Evaluations)
- Added tumor biopsy requirement at screening if the patient has transformed diffuse Large B-cell lymphoma (tDLBCL) and at disease progression (Appendix A Schedules of Evaluations)
- Updated sponsor name from Juno Therapeutics, Inc. to "the Sponsor" throughout the text
- Corrected misspellings, style, and formatting