Protocol Title:	The ROCKET Study: A Phase 2, Single-arm, Multicenter Trial to Determine the Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B Cell Acute Lymphoblastic Leukemia
Protocol Number:	015001 Amendment 5.1
NCT Number:	NCT02535364
Release Date:	14 July 2016

DISCLOSURE

REDACTED PROTOCOL

JCAR15 Protocol 015001 Amendment 5.1

The ROCKET Study: A Phase 2, Single-arm, Multicenter Trial to Determine the Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

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The ROCKET Study: A Phase 2, Single-arm, Multicenter Trial to Determine the Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Protocol Number: 015001 Amendment 5.1

Release Date: 14 July 2016

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PROTOCOL SIGNATURE PAGE

A Phase 2, Single-arm, Multicenter Trial to Determine the Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Sponsor Signatures: Date:

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the Declaration of Helsinki, the International Conference on Harmonization E6 Guideline for Good Clinical Practice, US FDA regulations, Institutional Review Board regulations, and all national, state and local laws of the pertinent regulatory authorities.

_____ _____

Investigator Printed Name Date

_____

Investigator Signature

PROTOCOL SYNOPSIS

Protocol Number: 015001	**Product Name:** JCAR015
Protocol Title: A Phase 2, Single-arm, Multicenter Trial to Determine the Efficacy and Safety of JCAR015 in Adult Subjects with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia	
Sponsor: Juno Therapeutics, Inc.	**Study Phase:** Phase 2

Rationale:

The outcome for adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) remains poor. For the subset of patients who are eligible for allogeneic hematopoietic stem cell transplant (HSCT) and have an available donor, the 5-year overall survival is estimated at approximately 25%. Those patients who are unable to undergo HSCT have a 5-year overall survival of less than 5%. Similarly, patients with relapsed disease following transplant have a dismal outcome due to the fact that either conventional chemotherapy or repeat allogeneic transplant is typically ineffective, and both approaches are accompanied by high rates of treatment-associated morbidity and mortality.

The development of CD19-specific chimeric antigen receptor (CAR) T cells to target CD19+ cancer cells, such as JCAR015, represents a new approach to the treatment of CD19+ B-cell malignancies. Using this approach, autologous T cells can be genetically modified to target leukemia cells through the expression of retroviral vector-transduced genes encoding CD19-specific CARs. The clinical experience to date with CD19-directed CAR T cells has shown this therapy to have potent anti-leukemia activity in both adult and pediatric patients.

Study Objectives:

Primary:

- To evaluate the efficacy of JCAR015 as measured by overall remission rate (ORR) after the final JCAR015 infusion in subjects with morphologic evidence of disease, based on independent review committee (IRC) assessment

Secondary:

1. To evaluate the duration of remission
2. To evaluate the percentage of subjects who achieve a complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with no evidence of minimal residual disease (MRD) in the bone marrow
3. To evaluate the safety and tolerability of JCAR015 therapy
4. To evaluate disease control (relapse-free survival, event-free survival, and overall survival)
5. To characterize the cellular pharmacokinetic (PK) profile of JCAR015, including the quantity and persistence in the peripheral blood and bone marrow
6. To characterize the prevalence and incidence of humoral immune responses to JCAR015
7. To evaluate the ORR at Month 6 following the final JCAR015 infusion
8. To compare the safety and tolerability of the JCAR015 cell product with the Memorial Sloan Kettering Cancer Center (MSKCC) 1928z CAR T cell product
9. To evaluate the percentage of subjects who achieve a morphologic remission within 6 months after the final JCAR015 infusion and then proceed to HSCT

Study Design: This is a single-arm, multicenter, Phase 2 study to determine the efficacy and safety of JCAR015 in adult subjects with morphologic relapsed or refractory (R/R) B-cell ALL. The study is divided into two sequential parts, Part A and Part B; subjects will be screened and will provide informed consent before initiating any study procedures in Part A of the study.

In Part A, subjects will undergo leukapheresis to enable T cell product generation and will then receive cytoreductive chemotherapy (and/or supportive care, at the Investigator's discretion) while the JCAR015 cell product is being manufactured. Upon recovery from any toxicities or illnesses arising during Part A and upon availability of JCAR015 cell product, subjects with evidence of hematopoietic recovery or refractory leukemia as assessed by peripheral counts will undergo a bone marrow examination to assess the burden of disease (CR or morphologic disease). Eligible subjects will proceed to Part B of the study. Subjects without evidence of hematopoietic recovery will continue to be monitored for evidence of marrow recovery or morphologic relapse.

In Part B, eligible subjects will receive a course of treatment consisting of lymphodepleting chemotherapy with cyclophosphamide and two infusions of JCAR015 cell product, administered 14 to 28 days apart. Response will be determined at 28 days following the final JCAR015 infusion.

Subjects treated in Part B of the study will be analyzed in two distinct groups (Group 1 and Group 2) based on their disease status prior to JCAR015 treatment (morphologic evidence of disease or CR [with presumed MRD], respectively). The primary efficacy analysis will be conducted in subjects with morphologic evidence of leukemia at the time of JCAR015 infusion (Group 1) who receive lymphodepleting chemotherapy with cyclophosphamide alone. Subjects who achieve a morphologic CR or CRi after cytoreductive chemotherapy will not be included in the primary analysis but will be included in the secondary efficacy, safety, manufacturing, and exploratory analyses (Group 2).

Bone marrow examinations will be repeated at Months 3, 6, and 12 after the final JCAR015 infusion, or until the subject requires alternative therapy for his or her disease. Response assessment will utilize guidelines based on Cheson et al. (Cheson 2003) and National Comprehensive Cancer Network (NCCN) ALL Guidelines (National Comprehensive Cancer Network 2014). Safety, relapse, and survival will be assessed until the end of the treatment and primary follow-up phase (12 months after the final JCAR015 infusion). Post-study follow-up for survival, relapse, long-term toxicity, and viral vector safety and persistence will continue under a separate long-term follow-up (LTFU) protocol for up to 15 years after the final JCAR015 infusion as per health authority regulatory guidelines.

Study Population: The target patient population consists of adult subjects with B-cell ALL with relapsed or refractory disease. Approximately 110 subjects will be enrolled to ensure that a minimum of 50 subjects with morphologic evidence of disease are treated with JCAR015 following lymphodepleting chemotherapy with cyclophosphamide alone.

Inclusion/Exclusion Criteria for Part A (see Section 5.2 for entry criteria for Part B)

Inclusion criteria:

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent
3. Diagnosis of B-cell ALL by flow cytometry
4. Relapsed or refractory disease, defined as:
   a. First or greater bone marrow relapse from CR, OR
   b. Any bone marrow relapse after allogeneic HSCT; subjects must be at least 100 days from HSCT (i.e., Day 0, receipt of hematopoietic stem cells) at the time of screening and off immunosuppressant medication for at least 1 month at the time of screening (with the exception of low-dose steroids [≤ 20 mg prednisone or equivalent]), and have no active graft versus host disease (GVHD), OR
   c. Refractory ALL, defined by not having achieved a CR or CRi after two attempts at remission induction using standard regimens, OR
   d. Philadelphia chromosome positive (Ph+) B-cell ALL if subjects are intolerant to or ineligible for tyrosine kinase inhibitor (TKI) therapy, OR have progressed after at least one line of TKI therapy

5. Bone marrow with morphological evidence of disease (≥ 5% blasts by morphology)
6. Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) from a sample obtained from the current relapse within 2 months of screening
7. Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2 at the time of screening
8. Adequate organ function, defined as:
   a. Serum creatinine ≤ 1.5 × age-adjusted upper limit of normal (ULN) OR calculated creatinine clearance (Cockcroft and Gault) > 30 mL/min/1.73 m^2
   b. Alanine aminotransferase (ALT) ≤ 5 × ULN (or ≤ 8 × ULN for subjects with leukemic infiltration of the liver) and direct bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with leukemic infiltration of the liver)
   c. Adequate pulmonary function, defined as ≤ Grade 1 dyspnea and SaO_2 ≥ 92% on room air
   d. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) performed within 1 month of enrollment
9. Adequate central or peripheral vascular access for leukapheresis procedure
10. Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use highly effective methods of contraception during the entire study period (Part A through 12 months after the final JCAR015 infusion). Women of reproductive potential must have a negative serum beta human chorionic gonadotropin (ß-hCG) pregnancy test result within 7 days prior to the first dose of cytoreductive chemotherapy.
11. Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method during the entire study period (Part A through 12 months after the final JCAR015 infusion).

Exclusion criteria:

1. Isolated extramedullary disease relapse
2. Concomitant genetic syndrome such as Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known bone marrow failure syndrome
3. Burkitt's lymphoma/leukemia or chronic myelogenous leukemia (CML) lymphoid blast crisis (p210 BCR-ABL+)
4. Prior malignancy, unless treated with curative intent and with no evidence of active disease present for > 5 years before screening, with the following exceptions:
   a. Subjects with Stage I breast cancer that has been completely and successfully treated, requiring no therapy or only anti-hormonal therapy
   b. Subjects with T1N0M0 or T2N0M0 colorectal cancer who have been completely and successfully resected and who are disease-free for > 2 years prior to screening
   c. Subjects with indolent prostate cancer, defined as clinical stage T1 or T2a, Gleason score ≤ 6, and prostate-specific antigen (PSA) < 10 ng/mL, requiring no therapy or only anti-hormonal therapy
   d. Subjects with a history of basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix, fully resected, and with no evidence of active disease
5. Treatment with any prior gene therapy product
6. Active hepatitis B, active hepatitis C, or any human immunodeficiency virus (HIV) infection at the time of screening
7. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) at the time of screening
8. Presence of Grade II-IV (Glucksberg) or B-D (IBMTR) acute or extensive chronic GVHD at the time of screening
9. Active central nervous system (CNS) involvement by malignancy, defined as CNS-3 per NCCN guidelines. Subjects with a history of CNS disease that has been effectively treated (defined as one documented negative cerebrospinal fluid [CSF] evaluation within 1 month prior to screening) will be eligible.

10. History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
11. History or presence of clinically relevant CNS pathology such as epilepsy, generalized seizure disorder, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
12. Participation in an investigational research study using an investigational agent within 30 days of screening, with the exception of investigational anti-infective agents (e.g., antibacterial, antifungal, antiviral)
13. History of treatment with a murine-derived biological product (unless subject has been shown to be negative for human-anti-mouse antibodies [HAMA] prior to or during screening). Prior use of blinatumomab is permitted (provided there is evidence of CD19 expression per Inclusion Criterion #6). Chimeric biological products (e.g., rituximab) are not considered murine for the purpose of this protocol.
14. Pregnant or nursing (lactating) women
15. Use of any of the following medications:
    a. Steroids: Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) are prohibited within 7 days prior to leukapheresis. Physiologic replacement dosing of steroids (≤ 12 mg/m^2/day hydrocortisone or equivalent [≤ 3 mg/m^2/day prednisone or ≤ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids and intrathecal steroids for CNS relapse prophylaxis are permitted.
    b. Allogeneic cellular therapy: Donor lymphocyte infusions (DLI) are prohibited within 4 weeks prior to leukapheresis
    c. GVHD therapies: Any drug used for GVHD within 4 weeks prior to leukapheresis, e.g., calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate mofetil, rapamycin, thalidomide, immunosuppressive antibodies (such as anti-CD20 [rituximab], anti-tumor necrosis factor-α [TNFα], anti-interleukin-6 [IL-6], or anti-interleukin-6 receptor [IL-6R])
    d. Chemotherapies: Salvage chemotherapy (e.g., cytosine arabinoside > 100 mg/m^2/day, anthracyclines, and cyclophosphamide) must be stopped at least 1 week prior to leukapheresis
16. Treatment with alemtuzumab within 6 months prior to leukapheresis, or treatment with clofarabine or cladribine within 3 months prior to leukapheresis
17. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or subject unwillingness or inability to follow the procedures required in the protocol

Test Product, Dose, and Mode of Administration: JCAR015 cell product consists of autologous CD3+, CD4+ and CD8+ T cells retroviral vector-transduced with a CD19-specific CAR (1928z) composed of a single chain variable fragment (scFv) derived from a murine CD19-specific monoclonal antibody (mAb) (SJ25C1), the transmembrane and intracellular signaling domains of CD28, and the cytoplasmic signaling domain of CD3ζ.

No study product will be administered in Part A. In Part B, JCAR015 will be administered as two intravenous (IV) infusions, administered 14 to 28 days apart. The first infusion (Dose #1) will be administered at a target dose of 1 × 10^6 JCAR015 cells/kg and preceded 2 to 5 days earlier by lymphodepleting chemotherapy with a single dose of 1.0-3.0 g/m^2 IV cyclophosphamide. The second infusion (Dose #2) will be administered at a target dose of 3 × 10^6 JCAR015 cells/kg; subjects whose white blood cell (WBC) count ≥ 1000/μL may receive a second dose of cyclophosphamide 2 to 5 days prior to this infusion at the discretion of the Investigator.

Efficacy Assessments:

Primary: Disease assessments by bone marrow examination (aspirate and biopsy for morphologic assessment) will be performed at 28 days after completion of the final infusion of JCAR015 (i.e., Dose #2 for subjects that complete JCAR015 treatment and Dose #1 for subjects that receive only one dose). Repeat bone marrow examinations will be performed at Months 3, 6, and 12 after the final JCAR015 infusion, or until the subject

requires alternative therapy for his or her disease.

Secondary: Clinical response will be assessed according to NCCN guidelines for ALL (National Comprehensive Cancer Network 2014) and the International Working Group (IWG) guidelines for acute myeloid leukemia (Cheson 2003) based on assessments of the bone marrow and peripheral blood, physical examination, evaluation of central nervous system (CNS) symptoms, and examination of the cerebrospinal fluid (CSF). Minimal residual disease assessment will be performed using IgH gene sequencing methodology, as described in the 015001 Central Laboratory Manual, to assess depth of remission and to describe the quantity, kinetics, immunophenotype, and distribution of malignant clones before and after JCAR015 infusion.

Safety Assessments:

Safety will be evaluated based on incidence of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities (type, frequency, and severity). Adverse events of special interest (AESI) will include cytokine release syndrome (CRS), neurological toxicity, macrophage activation syndrome, organ dysfunction, hemophagocytic lymphohistiocytosis (HLH) symptoms, tumor lysis syndrome, and allergic reaction.

Safety monitoring boundaries based on the incidence of Grade ≥ 3 JCAR015-related AESI are established using a Bayesian framework (Thall 1994, Yao 2013) 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 data safety monitoring board (DSMB) meeting will be held to review the data. Enrollment will remain paused pending the DSMB's recommendations.

Pharmacokinetics Assessments:

The cellular PK profile of JCAR015 (e.g., Cmax, Tmax, and AUC), expansion of JCAR015, and duration of persistence of JCAR015 will be evaluated.

Statistical Methods:

Analysis sets: Appropriate data analysis sets will be defined. The primary efficacy analysis set will include all subjects with morphologic evidence of leukemia, as determined by an IRC, at the time of JCAR015 infusion who receive lymphodepleting chemotherapy with cyclophosphamide alone and at least one dose of JCAR015. The primary efficacy analysis set will be used for the primary analyses of ORR and DOR.
A JCAR015-treated analysis set will include all subjects who receive at least one dose of JCAR015. The JCAR015-treated analysis set will be used for the safety analyses and some efficacy endpoint analyses. Other analysis sets (screened, enrolled, JCAR015-treated morphological disease analysis set, per protocol [PP], pharmacokinetic, and biomarker) will be used for certain analyses as well.

Primary endpoint: The primary efficacy endpoint is ORR, which is the proportion of subjects with CR or CRi as determined by the IRC after the final JCAR015 infusion (i.e., Dose #2 for subjects who complete JCAR015 treatment and Dose #1 for subjects who receive only one dose of JCAR015). The primary analysis will be carried out after all subjects in the primary efficacy analysis set are followed for at least 6 months from the start of Part B or have discontinued the study due to any reason. Updated efficacy and safety data will be summarized after all subjects have completed or discontinued the study.

The primary efficacy analysis will be performed by testing the null hypothesis of ORR ≤ 20% against the alternative hypothesis that the ORR > 20% at an overall 1-sided 2.5% level of significance, powered for ORR of 50%. The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. The study will be considered successful if the lower bound of the 2-sided 95% exact confidence interval for ORR is greater than 20%, such that the null hypothesis can be rejected.

Sensitivity analyses will be performed based on the PP analysis set using the same analysis method as described above. Additional sensitivity analysis will be performed using the ORR assessed by the Investigators based on the primary efficacy analysis set.

Secondary endpoints: Analysis of secondary endpoints will be presented using descriptive statistics. For continuous variables, sample size, mean, standard deviation or standard error, 95% confidence interval (CI) on the mean, median, minimum, and maximum for continuous variables will be presented. For categorical variables, descriptive summaries will include number, percentage, and 95% CI on the percentage. Cumulative

incidence functions (CIFs), Kaplan-Meier (KM) curves, and median time to event will be presented for time-to-event variables, if appropriate.

Information regarding AEs and laboratory abnormalities will be listed and summarized for subjects included in the JCAR015-treated analysis set.

Sample size: In a previous Phase 2 study of vincristine sulfate liposomal injection (HBS407) in adult subjects with Ph- ALL in second or greater relapse, the ORR (CR + CRi as determined by an IRC) was 15.4% (95% CI [7.6%, 24.5%]). Based on the null hypothesis of ORR ≤ 20% and an alternative hypothesis of ORR=50%, 50 subjects in the primary efficacy analysis set will provide > 95% power to demonstrate statistical significance for a 1-sided significance level of 0.025 based on an exact test and will provide an ample safety database.

An interim analysis is planned based on approximately ten subjects in the JCAR015-treated morphological disease analysis set. This interim analysis will assess analytical and clinical comparability between the JCAR015 cell product used in this study and the 1928z CAR T-cell product used in the ongoing Phase 1 study (MSKCC Protocol 09-114).

Assuming that 15% of subjects enrolled on Part A will not be infused with JCAR015 due to reasons such as manufacturing failure or worsening of subject's medical condition and 25% of subjects enrolled on Part A will achieve a CR from cytoreductive chemotherapy and be treated in Group 2 of Part B, approximately 110 subjects need to be enrolled to ensure that a minimum of 50 subjects are included in the primary efficacy analysis set.

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LIST OF ABBREVIATIONS

AAPC	artificial antigen presenting cells
AE	adverse event
AESI	adverse event(s) of special interest
AKI	acute kidney injury
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibodies
AUC	area under the curve
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BMT	bone marrow transplant
BOR	best overall response
CAR	chimeric antigen receptor
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIF	cumulative incidence function
CLL	chronic lymphocytic leukemia
Cmax	maximum concentration
CMC	Chemistry, Manufacturing, and Controls
CML	chronic myelogenous leukemia
CNS	central nervous system
CR	complete response or complete remission
CRA	clinical research associate
CRF	case report form
CRi	complete remission with incomplete blood count recovery
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
CTL	cytotoxic T lymphocyte
CVC	central venous catheter
DIC	disseminated intravascular coagulation
DLI	donor lymphocyte infusions
DMSO	dimethyl sulfoxide
DOR	duration of remission
DSMB	Data Safety Monitoring Board
DSMP	Data Safety and Monitoring Plan
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEG	electroencephalogram
EFS	event-free survival
EOS	end-of-study

FDA	Food and Drug Administration
FDAMA	Food and Drug Modernization Act
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
GVHD	graft versus host disease
HAMA	human anti-mouse antibodies
ß-hCG	beta human chorionic gonadotropin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoetic stem cell transplant
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IEC	independent Ethics Committee
IFNγ	interferon gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IgH	immunoglobulin H
IgM	immunoglobulin M
IHC	immunohistochemistry
IL	interleukin
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IND	Investigational New Drug application
IRB	Institutional Review Board
IRC	independent review committee
IV	intravenous(ly)
IVIG	intravenous immunoglobulin
JOIN	Juno Order Identification Number
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LTR	long terminal repeat
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRD	minimal residual disease
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MUGA	multiple uptake gated acquisition
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
NIH	National Institutes of Health
NYHA	New York Heart Association
OBA	Office of Biotechnology Activities
ORR	overall remission rate
OS	overall survival

OSHA	Occupational Safety and Health Administration
PBMC	peripheral blood mononuclear cell
PCP	pneumocystis jiroveci pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamics
Ph-	Philadelphia chromosome negative
Ph+	Philadelphia chromosome positive
PK	pharmacokinetic(s)
PO	per oral
PP	per protocol
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
qPCR	quantitative polymerase chain reaction
RAC	Recombinant DNA Advisory Committee
RCR	replication-competent retrovirus
RFS	relapse-free survival
R/R	relapsed or refractory
SAE	serious adverse event
scFv	single chain variable fragment
SCID	severe combined immunodeficiency
sCRS	severe cytokine release syndrome
SD	standard deviation
SDF-1	stromal cell-derived factor 1
SE	standard error
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SNP	single nucleotide polymorphism
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TNFα	tumor necrosis factor-α
ULN	upper limit of normal
VLSI	vincristine sulfate liposomal injection
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Overview of B-Cell Acute Lymphoblastic Leukemia

There are an estimated 6,000 new cases of B-cell acute lymphoblastic leukemia (ALL) diagnosed in the United States annually (Siegel 2014). Although initial remission rates in response to front-line therapy are in the range of 85% to 90%, approximately 60% to 70% of adult patients will relapse or develop chemotherapy-refractory disease. Overall long-term survival rates (i.e., ≥ 5 years) for adult patients diagnosed with B-cell ALL are approximately 40% to 50%, with survival rates decreasing with increasing patient age (Gokbuget 2009, Bassan 2011, Gokbuget 2012). Patients who relapse following first-line chemotherapy have even poorer outcomes; only 30% to 40% of such patients achieve a second remission with salvage chemotherapy (Thomas 1999, Fielding 2007, Tavernier 2007, Gokbuget 2012). Moreover, remissions following first salvage chemotherapy are usually short (2 to 7 months), with a relapse rate of greater than 70% (Welborn 1994, Bassan 1996, Weiss 1997, Garcia-Manero 2001, Fielding 2007, Tavernier 2007). Salvage chemotherapy is not curative; the median overall survival (OS) in the relapsed population is in the range of 3 to 6 months (Fielding 2007, Tavernier 2007, O'Brien 2008, Kantarjian 2010).

The only potentially curative option currently available for patients with relapsed B-cell ALL is allogeneic hematopoietic stem cell transplantation (HSCT). However, the ability to achieve a second or greater remission, eligibility requirements, donor availability, and treatment-related mortality associated with HSCT limit its application to patients. Patients with refractory B-cell ALL (those never achieving a complete response [CR]) have a dismal prognosis, and these patients are typically ineligible for HSCT. Thus, additional options are needed in relapsed or refractory (R/R) B-cell ALL. This protocol will evaluate the use of a novel cellular therapy, termed chimeric antigen receptor (CAR) T cells, which target CD19, a commonly expressed cell surface marker on B-cell ALL.

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). CD19 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 in all stages of B lineage cells and in the vast majority of precursor B-cells in patients with ALL. Importantly, the CD19 antigen is not expressed on any normal tissue apart from normal B lineage cells and is not expressed in hematopoietic stem cells. Therefore, depletion of normal B cells is the only anticipated on-target toxicity, minimizing the risk of bone marrow toxicity (Brentjens 2011, Kalos 2011, Porter 2011).

1.3 CD19–Targeted Chimeric Antigen Receptors

The development of CD19-specific CAR T cells to target CD19+ cells represents a new targeted approach for CD19+ malignancies. The CAR is a fusion protein composed of several elements, including an extracellular binding domain (single chain variable fragment [scFv]) that binds CD19, a transmembrane domain, and intracellular endodomains that provide activation signaling to the T cell after target cell engagement by the binding domain.

Production of CAR T cells requires autologous T cells to be genetically modified by ex vivo transduction using a recombinant gammaretroviral vector containing the CAR RNA sequence. Transduced T cells express the CAR on the cell surface and are effectively redirected toward recognition and lysis of CD19-expressing target cells including leukemia cells. Autologous CAR T cells may be generated and expanded from a patient's leukapheresis-derived peripheral blood mononuclear cells (PBMCs) and subsequently cryopreserved. The CAR T cells can later be thawed and administered intravenously (IV) to the same patient.

To date, multiple CAR constructs targeting both solid tumors and hematological malignancies have been described (Davila 2014, Maude 2014, Kochenderfer 2015, Lee 2015b). CD19-targeted CARs have demonstrated encouraging anti-leukemic clinical activity in relapsed or refractory adult and pediatric patients with B-cell ALL and other B-cell malignancies (Davila 2014, Maude 2014, Kochenderfer 2015, Lee 2015b). These initial clinical studies have also demonstrated a defined set of toxicities that are often associated with in vivo CAR T cell expansion, including cytokine release syndrome (CRS) and neurotoxicity, with limited autoimmune, marrow, or graft versus host disease (GVHD) complications observed.

1.4 Investigational Product: JCAR015

JCAR015 is derived from CD4+ and CD8+ T cells selected from PBMCs. The T cells are genetically modified ex vivo with a gene encoding a CAR specific for the CD19 antigen (1928z). The 1928z CAR consists of an scFv derived from a murine CD19-specific mAb (SJ25C1) fused to the CD28 transmembrane and intracellular signaling domains and the cytoplasmic signaling domain of CD3ζ. Unique to JCAR015 are the binding domain sequences, which, while murine in derivation, are immunologically distinct from the scFv binding domain sequences used in other published CAR constructs that use the FMC63 binding domain. Thus, in addition to use in B-cell ALL patients, JCAR015 may be effective in individuals who have developed immune responses to other CAR constructs.

The JCAR015 development program builds upon the previous development of 1928z CAR T cells at Memorial Sloan Kettering Cancer Center (MSKCC). JCAR015 CAR T cells utilize the same CAR gene (1928z) as the 1928z CAR T cells under investigation at MSKCC. Preclinical studies have demonstrated comparable in vitro and in vivo efficacy between JCAR015 and 1928z CAR T cells. Within this Phase 2 protocol, 1928z CAR T cells are referred to separately from JCAR015 CAR T cells to acknowledge manufacturing differences between the 1928z CAR T cell investigational drug product and the JCAR015 investigational drug product.

Significant clinical activity of 1928z CAR T cells has been demonstrated in a single-institution Phase 1 study at MSKCC (Protocol 09-114; NCT01044069), as evidenced by the achievement of a high CR rate in patients with relapsed/refractory B-cell ALL. As of 03 February 2015, a total of 33 subjects with B-cell ALL have been treated with 1928z CAR T cells. The median age at infusion was 54 years (range, 22-74).

Of the 33 subjects treated, 32 subjects were evaluable for efficacy assessment. At the time of CAR T cell infusion, 17 of 33 subjects had morphologic disease (5%–100% blasts in the bone marrow) and the remaining 16 subjects had minimal residual disease (MRD) (<5% blasts). Overall, 29 of 32 (91%) subjects evaluable for response assessment achieved a CR after CAR T cell infusion (see Table 1); of 28 subjects who achieved a CR and were evaluable for MRD assessment, 23 subjects

(82%) achieved an MRD-negative CR. Eleven of the 32 (34%) subjects successfully underwent allogeneic HSCT following CAR T cell therapy. Median follow-up was 5 months (range, 1-38 months). Thirteen subjects remain disease-free (nine subjects without HSCT). Responses appear durable with seven subjects remaining disease-free >1 year. Eleven subjects relapsed during follow-up, including three subjects who relapsed post-HSCT. Among 32 subjects, median OS is 8.5 months, and survival rate at 6 months is 57% (95% confidence interval [CI], 36%–74%).

Overall, seven of 33 (21%) subjects developed severe cytokine release syndrome (sCRS); seven of 17 (41%) subjects with morphologic disease at the time of infusion developed sCRS with or without neurological symptoms that required intervention with an IL-6R antagonist, corticosteroid, or IL-6R antagonist + corticosteroid. Severe CRS was defined as requiring vasopressors and/or mechanical ventilation for hypoxia. In total, ten of 33 (30%) subjects developed Grade 3/4 neurological toxicities. Notably, neurological symptoms could occur independently of sCRS. In the vast majority of subjects, neurological symptoms have been fully reversible; however, one individual in the Phase 1 study developed status epilepticus (see Section 5.3 of Investigator Brochure). No GVHD exacerbation was reported in the Phase 1 study.

Table 1: Summary of Clinical Data (MSKCC Protocol 09-114)

	Disease Burden		
	Low[a] (n=16)	**High[a] (n=17)[b]**	**Total**
Complete remission[c]	16/16 (100%)	13/16 (81%)	29/32 (91%)
Complete molecular remission[d]	12/16 (75%)	11/12[e] (92%)	23/28[e] (82%)
Severe CRS	0/16 (0%)	7/17 (41%)	7/33 (21%)
≥ Grade 3 neurotoxicity	3/16 (19%)	7/17 (41%)	10/33 (30%)

a Low burden = marrow blasts < 5%; high burden = marrow blasts ≥ 5%
b Includes two subjects with extra-medullary disease only
c Includes both CR and CRi
d Measured by flow cytometry or polymerase chain reaction (PCR)
e One subject with CR was not evaluable for MRD

A summary of the important toxicities expected with JCAR015 administration (e.g., CRS and neurotoxicity) and guidelines for management of these toxicities are provided in Section 7.

Nonclinical data, and updated clinical data from MSKCC Protocol 09-114, are provided in the JCAR015 Investigator's Brochure (IB).

1.5 Clinical Experience on the 015001 Protocol

Protocol 015001 was amended on 18 December 2015 to allow for the use of cyclophosphamide in combination with fludarabine (30-60 mg/kg cyclophosphamide IV for 1 day followed by fludarabine 25 mg/m^2/day IV daily for 3 days) as lymphodepleting chemotherapy prior to administration of JCAR015. Use of this conditioning regimen was implemented on 09 May 2016, and four subjects were treated with this regimen through 01 June 2016. Of these four subjects, one subject experienced Grade 5 severe CRS in addition to Grade 5 cerebral edema and brainstem herniation 8 days after JCAR015 infusion.

Following this event, the guidelines for management of CRS were updated and investigators were instructed to ensure prompt medical intervention for subjects with Grade 2 CRS, especially for those with early onset of Grade 2 or higher CRS symptoms (i.e., within 96 hours of infusion), characterized by high fevers, hypotension, neurologic symptoms, and/or rapid elevation in CRP and/or ferritin. Following implementation of these revised guidelines, between 01 June 2016 and 30 June 2016, four additional subjects were treated with JCAR015 following lymphodepletion with cyclophosphamide in combination with fludarabine. All four of these subjects experienced severe (Grade 3 or greater) neurologic toxicity, including two subjects who had Grade 5 cerebral edema and brainstem herniation. Three of the four subjects developed early symptoms of CRS and were treated promptly as per the revised management guidelines.

Analysis of the eight subjects treated with JCAR015 following lymphodepletion with cyclophosphamide in combination with fludarabine demonstrated severe (Grade 3 or greater) neurologic toxicity in 7/8 (88%) subjects and severe CRS (Grade 3 or greater) in 1/8 (13%) subjects. By comparison, 14 subjects treated to date on Protocol 015001 with JCAR015 following lymphodepletion with cyclophosphamide alone revealed severe neurologic toxicity in 3/14 (21%) subjects and severe CRS in 2/14 (14%) subjects. In a univariate analysis of Grade 3 or greater versus Grade 2 or lower neurologic toxicity, the lymphodepleting regimen (fludarabine/cyclophosphamide versus cyclophosphamide alone; 88% versus 14%) was the most statistically significant clinical factor ($p = 0.006$) among the clinical variables examined. Furthermore, in a multivariate stepwise logistical regression analysis for Grade 3 or greater neurologic toxicity, lymphodepleting regimen was the only independent variable retained in the final model at a two-sided significance level of 0.1.

Of note, all three subjects who experienced Grade 5 neurologic toxicity were under the age of 30 years. However, an analysis of Grade 3 or neurologic toxicity for morphologic subjects treated to date with JCAR015 following lymphodepletion with cyclophosphamide alone showed an incidence of 0/5 (0%) (age range, 19-29 years). Similarly, on MSKCC Protocol 09-114, only 1/7 (14%) morphologic subjects under the age of 30 (age range, 24-30 years) had Grade 3 or greater neurologic toxicity. For all subjects on both studies, there were no instances of cerebral edema for any subject under the age of 30 who was treated with cyclophosphamide alone. Taken together, subject age does not appear to be a factor for severe neurologic toxicity with cyclophosphamide-only conditioning across these studies.

Finally, analysis of all subjects treated with CD19-directed CAR T cells across Juno Protocol 015001 and MSKCC Protocol 09-114 demonstrates a comparable rate of Grade 3 or greater neurologic toxicity for subjects treated with CAR T cells following lymphodepletion with cyclophosphamide alone (Table 2). Based on this analysis, and following a discussion with the Data Safety Monitoring Board (DSMB) and Food and Drug Administration (FDA), fludarabine/cyclophosphamide lymphodepleting chemotherapy has been removed per Amendment 5 of the protocol. Subjects will receive JCAR015 following lymphodepletion with cyclophosphamide alone.

Table 2: Toxicity in MSKCC Protocol 09-114 and Juno Protocol 015001

	Juno 015001 (data as of 01 July 2016)	**MSKCC 09-114** (data as of 01 May 2016)
	Morphologic Subjects Cyclophosphamide alone (N=14)	**Morphologic Subjects[b] Cyclophosphamide alone (N=23)**
sCRS	2 (14%)[a]	11 (48%)
Grade ≥3 neurotoxicity	3 (21%)	8 (35%)
Deaths due to toxicity	0	2 (9%)
First infusion, median cell dose (range) ($\times 10^6$/kg)	0.93 (0.65, 1.43)	2.52 (1.08, 4.32)[c]

[a] Data may be incomplete

[b] ≥5% blasts in the bone marrow or extramedullary disease

[c] Note that dosing in this study started with 3×10^6 CAR T cells/kg but was decreased to 1×10^6 CAR T cells/kg for subjects with morphologic disease

2 STUDY RATIONALE

This is a single-arm, multicenter, Phase 2 study to determine the efficacy and safety of JCAR015 in adult subjects with morphologic R/R B-cell ALL. The study is divided into two sequential parts, Part A and Part B. In Part A, subjects will undergo leukapheresis to enable T cell product generation and will then receive cytoreductive chemotherapy (and/or supportive care, at the Investigator's discretion) while the JCAR015 cell product is being manufactured. Upon recovery from any toxicities or any illnesses arising during Part A and upon availability of JCAR015 cell product, subjects with evidence of hematopoietic recovery as assessed by peripheral counts will undergo a bone marrow examination to assess the burden of disease (CR or morphologic disease). Eligible subjects will proceed to Part B of the study. Subjects without evidence of hematopoietic recovery will continue to be monitored for evidence of marrow recovery or morphologic relapse.

In Part B, eligible subjects will receive a course of treatment consisting of lymphodepleting chemotherapy and two infusions of JCAR015 T cells administered 14 to 28 days apart. The target dose for the first infusion is 1×10^6 JCAR015 cells/kg, and the target dose for the second infusion is 3×10^6 JCAR015 cells/kg. Response will be determined at 28 days following the final JCAR015 infusion.

Subjects treated in Part B of the study will be analyzed in two distinct groups based on their disease status prior to JCAR015 treatment (Group 1: morphologic evidence of disease; Group 2: CR with presumed MRD). The primary efficacy analysis will be conducted in subjects with morphologic evidence of leukemia at the time of JCAR015 infusion (Group 1) who receive lymphodepleting chemotherapy with cyclophosphamide alone. Subjects who achieve a morphologic CR or CRi after cytoreductive chemotherapy will not be included in the primary analysis but will be included in the secondary efficacy, safety, manufacturing, and exploratory analyses (Group 2).

Of note, several changes to the cell production process to accommodate a multicenter study have been implemented relative to the single-site Phase 1 process employed in the ongoing study at MSKCC. These process changes are not thought to pose a significant safety risk to subjects on this study. Nevertheless, this study will utilize multiple strategies to monitor and ensure subject safety including pre-specified pausing/stopping rules (Section 4.3.1), a continuous safety monitoring algorithm (Section 4.3.2), an interim analysis (Section 10.5.1), and a data safety monitoring board (Section 9.5).

2.1 Rationale for JCAR015 in Relapsed or Refractory B-cell ALL

Patients with relapsed or refractory B-cell ALL have extremely poor clinical outcomes with standard-of-care therapy (O'Brien 2008). 1928z CAR T cells have been shown in an ongoing Phase 1 study (MSKCC Protocol 09-114) to be capable of inducing CR in the vast majority of patients with morphologic disease (Davila 2014, Park 2014). Similarly, 1928z CAR T cells have been shown to convert patients in CR but with MRD to an MRD-negative state. The ability to achieve a remission for patients with chemorefractory disease, or a second or later remission for patients with relapsed disease, may enable these patients to undergo potentially curative allogeneic HSCT. Moreover, for patients with relapsed or refractory disease who are transplant-ineligible, achievement of a CR may extend leukemia-free and overall survival. Because CR is a clinically relevant endpoint in this population, a pivotal efficacy trial is warranted based on the existing Phase 1 data.

2.2 Rationale for Single-Arm Design

The single-arm study design is supported by the high response rate observed in current Phase 1 trials of 1928z CAR T cells and other CD19-directed CAR T cell products. Recent data indicate that these CAR T cell therapies are capable of inducing CR in 70% to 90% of patients with relapsed or refractory B-cell ALL (Davila 2014, Maude 2014, Park 2014, Lee 2015b). The standard-of-care for patients with relapsed or refractory B-cell ALL is currently supportive care or salvage chemotherapy (National Comprehensive Cancer Network 2014), which is not expected to be curative for the population under study given that historical CR rates in this population are < 20% (O'Brien 2008). The dramatic difference in response rates observed with 1928z CAR T cells and salvage chemotherapy in the relapsed/refractory treatment setting would prevent a randomized trial from meeting conditions of clinical equipoise.

2.3 Rationale for Use of Cytoreductive Chemotherapy (Part A)

The rationale for the use of cytoreductive chemotherapy in Part A of the study is multifold. First, patients with relapsed or refractory B-cell ALL typically have rapidly proliferating disease. Because leukapheresis and manufacturing of JCAR015 cell product requires approximately 3 weeks, it is expected that it will be necessary to provide chemotherapy to a majority of subjects as a means to control disease progression while the cell product is generated. Investigators maintain the option to provide supportive care or lower-intensity chemotherapy to subjects with less rapidly proliferating disease to avoid the toxicity of a multi-agent chemotherapy regimen. Second, subjects who receive salvage chemotherapy and continue to have morphologic evidence of disease will have been clearly demonstrated to have chemorefractory disease. As such, CR following JCAR015 infusion in these subjects will be solely attributable to the test article and not confounded by the effect of the last cycle of salvage chemotherapy. Third, cytoreductive therapy may reduce the marrow disease burden prior to JCAR015 infusion, which may in turn reduce the risk or severity of CRS. In addition, cytoreduction may facilitate access of CAR T cells to the marrow space and subsequent T cell engraftment, as CAR T cells may not be able to fully engraft and expand in the setting of a hypercellular bone marrow.

2.4 Rationale for Treating Subjects with MRD

The rationale for treating subjects with relapsed/refractory disease who achieve a CR following cytoreductive chemotherapy in Part A of the current study is based on existing data that such therapy is not curative, and data from the Phase 1 study of 1928z CAR T cells (MSKCC Protocol 09-114) showing that those subjects treated while in CR with MRD were able to be converted to a MRD-negative state. It is expected that an increase in the depth of remission may confer clinical benefit to the subjects, potentially by prolonging leukemia-free survival. Because the incidence of CRS has been shown in the ongoing Phase 1 study to be substantially lower in subjects with only MRD, the benefit:risk ratio favors treating MRD-positive patients who are at high risk for relapse (Davila 2014, Park 2014).

It is not possible to determine at the time of study entry whether or not subjects will achieve a CR from cytoreductive chemotherapy. However, because these subjects will have undergone leukapheresis and JCAR015 product generation, and also because subjects with MRD-only disease may receive some clinical benefit, these subjects will be provided the opportunity to receive

JCAR015. Because these subjects are already in a morphologic CR at the time of JCAR015 infusion, they are not evaluable for the primary efficacy endpoint and will be evaluated separately.

2.5 Rationale for Lymphodepleting Chemotherapy

It is widely believed that lymphodepleting chemotherapy improves engraftment of CAR T cells. Various lymphodepleting chemotherapy regimens have been investigated for CAR T cells, including cyclophosphamide monotherapy (Davila 2014), cyclophosphamide in combination with etoposide (Grupp 2013, Turtle 2014), and cyclophosphamide in combination with fludarabine (Kochenderfer 2015). For this protocol, single-agent cyclophosphamide at a dose range of 1.0 to 3.0 g/m^2 IV will be used for lymphodepletion (Brentjens 2013).

The dose range of cyclophosphamide was selected to provide investigators with the flexibility to select a dose that is clinically appropriate based on the subject's medical needs. A dose of 3.0 g/m^2 IV should be used, but the dose may be reduced as low as 1.0 g/m^2 IV if needed based on the subject's marrow reserve (e.g., lower dosing for subjects with limited marrow reserve and/or impaired renal or cardiac function and higher dosing for subjects with a large leukemic burden).

The mechanism by which T cell engraftment is facilitated by lymphodepleting chemotherapy is not fully understood. The rationale for combining adoptive T cell immunotherapy with lymphodepleting therapy is based on multiple lines of evidence. First, lymphodepleting chemotherapy may enhance adoptively transferred tumor specific T cells to proliferate in vivo through homeostatic proliferation (Grossman 2004, Stachel 2004). Second, chemotherapy may reduce or eliminate CD4$^+$CD25$^+$ regulatory T cells, which can suppress the function of tumor-targeted adoptively transferred T cells (Turk 2004). Third, lymphodepleting chemotherapy prior to adoptive T cell therapy may enhance the expression of stromal cell-derived factor 1 (SDF-1) in the bone marrow, enhancing the homing of modified T cells to the primary tumor site through binding of SDF-1 with CXCR-4 expressed on the T cell surface (Pinthus 2004). Finally, lymphodepleting chemotherapy may further reduce the subject's tumor burden and potentially lower the risk and severity of CRS.

2.6 Rationale for Dose Selection

The selection of dose and schedule for this study was based on three key observations from preclinical experiments and ongoing clinical studies of CD19-directed CAR T cells:

- An observed correlation between infused cell dose and duration of response/survival
- Observed correlations between burden of disease at the time of cell infusion and incidence of sCRS, and between infused cell dose and the incidence of severe neurotoxicity
- A correlation between cell persistence and duration of response

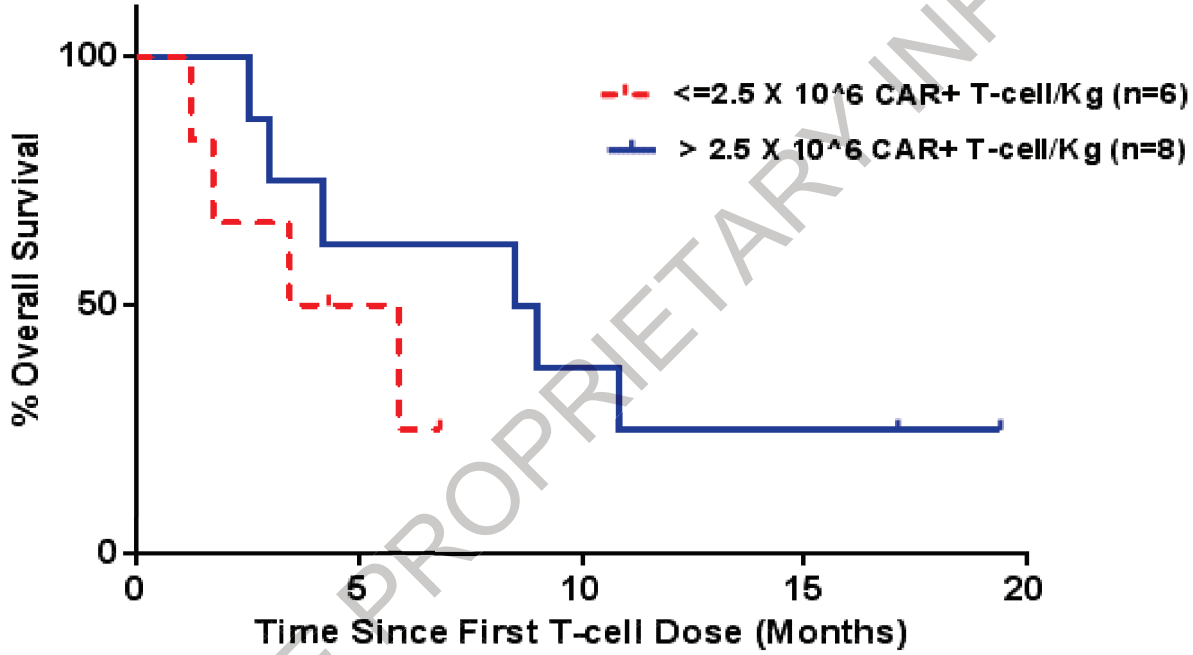
2.6.1 Relationship between Cell Dose and Response

Based on data collected to date in adult patients with ALL, there does not appear to be a clear dose-response relationship between the quantity of CAR T cells infused and achievement of morphologic remission. This is likely due to the ability of CAR T cells to expand exponentially in vivo post-infusion in response to antigen stimulus. As such, the number of CAR T cells following

expansion is expected to vary substantially between individuals owing to a variety of factors, including burden of disease at the time of infusion. Analysis of the available data, along with manufacturing feasibility, supports a threshold infused target dose of at least 1×10^6 JCAR015 cells/kg.

Contrary to the apparent lack of relationship between cell dose and overall response rate, a post hoc exploratory survival analysis from the ongoing Phase 1 study (MSKCC Protocol 09-114) showed a difference between dose and overall survival among subjects with morphologic evidence of disease at the time of CAR T cell infusion (Figure 1). In this study, data to date indicated a median overall survival of 4.7 months for subjects receiving a dose $\leq 2.5 \times 10^6$ CAR^+ T cells/kg compared to 8.7 months for subjects receiving $> 2.5 \times 10^6$ CAR^+ T cells/kg.

Figure 1: Overall Survival by Cell Dose Group in Subjects with Morphological Disease at the Time of CAR T Cell Infusion



Note: Excludes two subjects with morphological disease whose cell dose data were not available at the time of the analysis

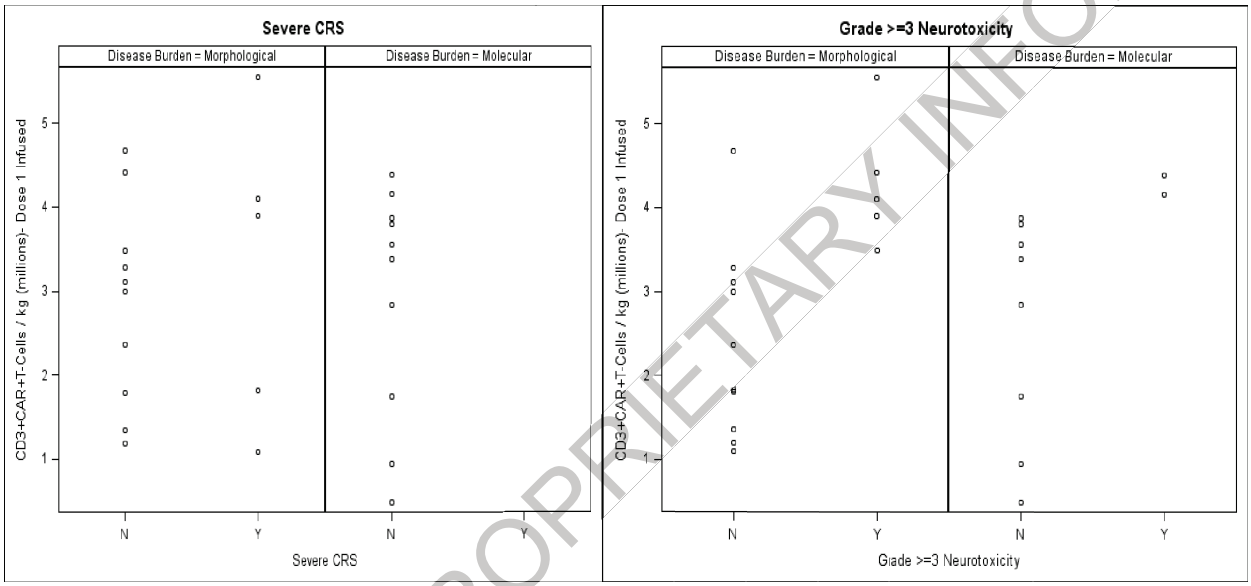
2.6.2 Relationship between Disease Burden, Cell Dose, and Toxicity

Studies of a CD19-specific CAR administered to subjects with ALL have suggested that a larger cytokine response and a higher risk of sCRS occur in subjects with large tumor burdens (i.e., morphologic evidence of disease) compared to subjects who are in morphologic remission with MRD at the time of CAR T cell infusion (Sadelain 2013). Data from the ongoing MSKCC Phase 1 study have suggested that subjects in a morphologic CR with MRD are able to tolerate higher doses of 1928z CAR T cells with a substantially lower risk of sCRS or severe neurotoxicity (Figure 2). To date, no subject in morphologic remission at the time of CAR T cell infusion has been

observed to experience sCRS, compared to seven of 17 subjects with morphologic disease at the time of infusion. Similarly, only three of 16 subjects in morphologic remission at the time of CAR T cell infusion have experienced ≥ Grade 3 neurotoxicity compared to 7 of 17 subjects with morphologic disease.

There does not appear to be a dose-toxicity relationship with regard to sCRS in subjects with morphologic disease at the time of CAR T cell infusion. There does, however, appear to be a correlation between cell dose and incidence of severe neurotoxicity that is independent of disease burden at T cell infusion. As seen in Figure 2, all subjects with morphologic evidence of disease at the time of CAR T cell infusion who experienced ≥ Grade 3 neurotoxicity received a cell dose ≥ 3.5×10^6 CAR^+ T cells/kg. Similarly, both subjects in a morphologic CR with MRD who experienced Grade 3 neurotoxicity received cell doses greater than 4.0×10^6 CAR^+ T cells/kg.

Figure 2: Correlation between Disease Status, Cell Dose, and Toxicity



Note: Only includes subjects whose cell dose data were available at the time of the analysis

2.6.3 Relationship between Cell Persistence and Duration of Response

Preclinical xenograft data demonstrated that the incidence of long-term survival with CD19-directed CAR T cell therapy increased from 18% with an upfront daily three-dose treatment schedule to 44% in a weekly treatment schedule (Brentjens 2007). This observation is consistent with data from clinical trials of other CD19-targeted CAR T cells suggesting that increased exposure to CAR T cells (i.e., cell persistence) is associated with increased duration of response (Maude 2014, Maus 2014). In addition, early data from other studies with CD19-targeted CAR T cells suggest a correlation between exposure to circulating CAR T cells and overall survival (Grupp 2013, Grupp 2014).

2.6.4 Rationale for Dose Schedule

Based on the observations described above, this protocol will administer two doses of JCAR015. Because the persistence of 1928z CAR T cells in the MSKCC Phase 1 study has been observed to

be approximately 10 to 15 days post-infusion, the second dose of JCAR015 will be administered at 14 to 28 days after the first infusion. Analysis of data from subjects with either morphologic MRD or morphologic relapse who were re-treated with a second dose of CAR T cells has indicated that this approach is safe, feasible, and clinically efficacious. It is expected that this dose schedule will result in increased exposure that will subsequently reduce MRD, increase duration of remission, and increase both leukemia-free and overall survival.

The first dose will consist of an initial infusion of JCAR015 at a target dose of 1×10^6 JCAR015 cells/kg. Upon recovery from any toxicities, a second infusion of JCAR015 will be administered at a higher target dose of 3×10^6 JCAR015 cells/kg 14 to 28 days following the first infusion with the expectation that subjects' disease burden will be substantially reduced following the first dose. This expectation is based on the very high CR rate (approximately 90%) observed following a single dose of 1928z CAR T cells in the ongoing MSKCC Phase 1 study, and data indicating the ability of 1928z CAR T cells to rapidly convert patients from an MRD-positive to MRD-negative state.

Data from the ongoing MSKCC Phase 1 study has shown that, to date, none of the four subjects who failed to achieve a CR after a dose of CAR T cells have experienced either CRS or neurotoxicity (Table 3). As such, it is thought that the risk from the second infusion is acceptable in subjects who do not respond to the first infusion, especially in the face of relapsed or refractory disease.

Table 3: sCRS and Neurotoxicity in Subjects without a Response to 1928z CAR T Cells Dose #1 in MSKCC Protocol 09-114

Subject ID	Bone marrow blast %	Dose #1 (CAR^+/kg)	sCRS	≥ Grade 3 Neurotox	Day of retreat	Bone marrow blast % at retreat	Dose #2 (CAR^+/kg)	sCRS	≥ Grade 3 Neurotox
	High	1.1×10^6	No	No	NA	NA	NA	NA	NA
	97%	3×10^6	No	No	Day 15	High	3.8×10^6	No	No
	EM only[a]	3×10^6	No	No	NA	NA	NA	NA	NA
	90%	4.3×10^6	No	No	Multiple	56%	3.3×10^6	No	No

a Extramedullary disease only

The interval between the first and second infusions was chosen to be sufficiently long to allow resolution of any CRS symptoms, but short enough to reduce the likelihood of a substantial immune response that could accelerate elimination of the JCAR015 cells. Finally, the use of a second infusion of cells will allow for more aggressive treatment of CRS with corticosteroids in patients with morphologic disease at the time of infusion, in that any impact of corticosteroids on the function or persistence of the first dose of JCAR015 cells will be compensated for by administration of a second dose.

3 STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for the study are presented in Table 4.

Table 4: Study Objectives and Endpoints

Objectives	Endpoints
Primary (Primary Efficacy Analysis Set)	
• To evaluate the efficacy of JCAR015 as measured by overall remission rate (ORR) after the final JCAR015 infusion in subjects with morphologic evidence of disease, based on independent review committee (IRC) assessment	• ORR, defined as the proportion of subjects with CR or complete remission with incomplete blood count recovery (CRi), as determined by examination of the bone marrow, peripheral blood, and cerebrospinal fluid (CSF), as well as physical examination and evaluation of central nervous system (CNS) symptoms.
Secondary	
1. To evaluate the duration of remission	• Duration of morphologic remission, defined as the time from achievement of morphologic CR or CRi, whichever occurs first, to morphologic relapse or death due to B-cell ALL • Duration of molecular remission, defined as the time from achievement of an MRD-negative CR or CRi, whichever occurs first, to molecular relapse (appearance of MRD) or morphologic relapse, or death due to B-cell ALL
2. To evaluate the percentage of subjects who achieve a CR or CRi with no evidence of MRD in the bone marrow (i.e., below the level of detection for the IgH gene sequencing)	• Percentage of subjects who achieve CR or CRi with an MRD-negative bone marrow, as assessed by IgH gene sequencing
3. To evaluate the safety and tolerability of JCAR015 therapy	• Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities

Objectives	Endpoints
4. To evaluate disease control	• Relapse-free survival, defined as the time from achievement of CR or CRi, whichever occurs first, to relapse or death due to any cause • Event-free survival, defined as the time from the date of the first JCAR015 infusion to death from any cause, relapse, or treatment failure, whichever occurs first • Overall survival, defined as the time from the date of the first JCAR015 infusion to date of death due to any reason
5. To characterize the cellular pharmacokinetic (PK) profile of JCAR015, including the quantity and persistence in the peripheral blood and bone marrow	• Cellular PK profile of JCAR015 (e.g., Cmax, Tmax, AUC) • Maximum expansion of JCAR015 • Duration of persistence of JCAR015
6. To characterize the prevalence and incidence of humoral immune responses to JCAR015	• Proportion of subjects developing anti-therapeutic antibodies (ATA)
7. To evaluate the ORR at Month 6 following the final JCAR015 infusion	• Percentage of subjects who achieve CR/CRi without HSCT from the time of the final JCAR015 infusion to the Month 6 post-infusion assessment
8. To compare the safety and tolerability of the JCAR015 cell product with the MSKCC 1928z CAR T cell product	• Type, frequency, and severity of treatment-emergent AEs and treatment-emergent AEs of special interest (AESI)
9. To evaluate the percentage of subjects who achieve a morphologic remission within 6 months after the final JCAR015 infusion and then proceed to HSCT	• Percentage of subjects who achieve a CR/CRi and then proceed to HSCT while in remission within 6 months after the final JCAR015 infusion
Exploratory	
1. To describe the change in the number of normal B lymphocytes over time following JCAR015 treatment	• Peripheral blood B cell counts
2. To describe the relationship between CD19 and CD22 expression on leukemic blasts at baseline, blast percentage, and/or bone marrow cellularity, and JCAR015 safety, PK, and efficacy	• Median CD19 and CD22 expression on leukemia blasts as assessed by a quantitative flow cytometry assay

Objectives	Endpoints
3. To describe the genomic and immunophenotypic profile of JCAR015 and resident immune cells following infusion	• Immunophenotypic profile of JCAR015 and resident immune cells as assessed by flow cytometry and genomic profile as assessed by RNA sequencing (RNA-Seq), targeted DNA sequencing, and whole genome/exome analysis
4. To characterize the incidence of anti-JCAR015 antibodies, and of a JCAR015-directed cytotoxic T lymphocytes (CTL) response (i.e., immunogenicity) after JCAR015 treatment	• Measurement of ATA and cellular immune response to JCAR015
5. To describe changes in the profile of soluble immune factors or inflammatory markers that may be associated sCRS, and the effect of corticosteroid and/or anti-cytokine therapy on this profile	• Profile of and change in profile of soluble immune factors in the blood (cytokines); changes in inflammatory markers associated with sCRS (i.e., C-reactive protein, serum ferritin)
6. To describe the effect of treatments directed at sCRS on duration and severity of sCRS, JCAR015 PK and pharmacodynamics (PD), JCAR015 cell persistence, and disease response	• Response and time to response of sCRS to interventions (e.g., time to fever reduction after treatment; proportion of subjects who respond to intervention within 24 hours based on CRS grade)
7. To describe the relationship between JCAR015 clinical characteristics (efficacy, safety, PK, and markers of intermediate efficacy) and JCAR015 product quality attributes and process performance attributes	• JCAR015 product characteristics (e.g., T cell subsets, transduction efficiency)
8. To describe the relationship between tumor burden, tumor response, cellular PK/PD, and sCRS	• Pattern and kinetics of CD4+ and CD8+ JCAR015 T cells post-infusion
9. To describe the relationship between clinical outcomes (disease response and safety) and genomic features of the underlying leukemia	• Gene expression profiling (e.g., RNA-Seq), targeted DNA sequencing, and whole genome/exome sequencing of leukemic blasts at baseline
10. To describe changes in immunophenotype, gene expression profiling, and/or DNA sequencing data between on-study baseline tumor data and on-study relapsed tumor data	• Gene expression profiling, targeted DNA sequencing, whole genome/exome sequencing, and immunophenotypic analysis of leukemic blasts at baseline, post-treatment, and relapse

Objectives	Endpoints
11. To describe changes in the tumor microenvironment components following JCAR015 treatment	• Gene expression profiling, targeted DNA sequencing, whole genome/exome sequencing, and/or immunophenotypic analysis of cells obtained from bone marrow aspirate and biopsy at baseline, post-treatment, and at relapse
12. To characterize changes in quality of life outcome measures and hospital resource utilization for subjects treated with JCAR015	• Subject-reported outcomes as measured by FACT-Leu questionnaire • Hospital resource utilization as measured by number of inpatient days, intensive care unit (ICU) days, and outpatient visits

4 STUDY DESIGN AND INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a single-arm, multicenter, Phase 2 study to determine the efficacy and safety of JCAR015 in adult subjects with morphologic relapsed or refractory (R/R) B-cell ALL. The study is divided into two sequential parts, Part A and Part B; subjects will be screened and will provide informed consent before initiating any study procedures in Part A of the study.

In Part A of the study, subjects will undergo leukapheresis to enable T cell product generation and will then receive cytoreductive chemotherapy (and/or supportive care, at the Investigator's discretion) while JCAR015 T cell product is being manufactured. Upon recovery from any toxicities or illnesses arising during Part A and upon notification of availability of JCAR015 cell product, subjects with evidence of hematopoietic recovery or refractory leukemia as assessed by peripheral counts will undergo a bone marrow examination to assess the burden of disease (morphologic remission or morphologic disease), as well as to collect specimens for biomarker evaluations. Depending on the level of marrow disease, subjects will be evaluated in one of two groups: Group 1 (morphologic disease, defined as ≥ 5% blasts in the bone marrow) or Group 2 (CR with presumed MRD, defined as < 5% blasts in the bone marrow). Subjects whose disease status cannot be ascertained by Day 42 following cytoreductive chemotherapy (i.e., those who have a hypoplastic, aplastic, or "recovery" marrow by Day 42) will be evaluated in Group 2. All subjects completing Part A will be re-assessed to ensure that Part B inclusion/exclusion criteria are met. Eligible subjects will proceed to Part B of the study.

In Part B of the study, eligible subjects will receive a course of treatment with JCAR015, consisting of lymphodepleting chemotherapy followed by two infusions of JCAR015, administered 14 to 28 days apart. Lymphodepleting chemotherapy will consist of a single dose of cyclophosphamide (1.0 to 3.0 g/m^2 IV). Use of this lymphodepleting regimen is based on the MSKCC (Protocol 09-114) Phase 1 study experience, and because of the significant experience with the use of this agent in facilitating adoptive immunotherapy (Brentjens 2013, Turtle 2015). Response will be determined at 28 days following the final JCAR015 infusion (i.e., Dose #2 for subjects that complete JCAR015 treatment or Dose #1 for subjects that receive only one dose of JCAR015). The primary efficacy analysis will be conducted in subjects with morphologic evidence of leukemia at the time of JCAR015 infusion (Group 1) who receive lymphodepleting chemotherapy with cyclophosphamide alone. Subjects in a morphologic CR or CRi at the time of JCAR015 infusion cannot be assessed for CR in response to JCAR015 and, as such, will not be included in the primary efficacy analysis. These subjects, along with those whose disease status cannot be determined on Day 42 of Part A (those with a hypoplastic, aplastic, or "recovery" marrow), will be included in the secondary efficacy, safety, manufacturing, and exploratory analyses (Group 2).

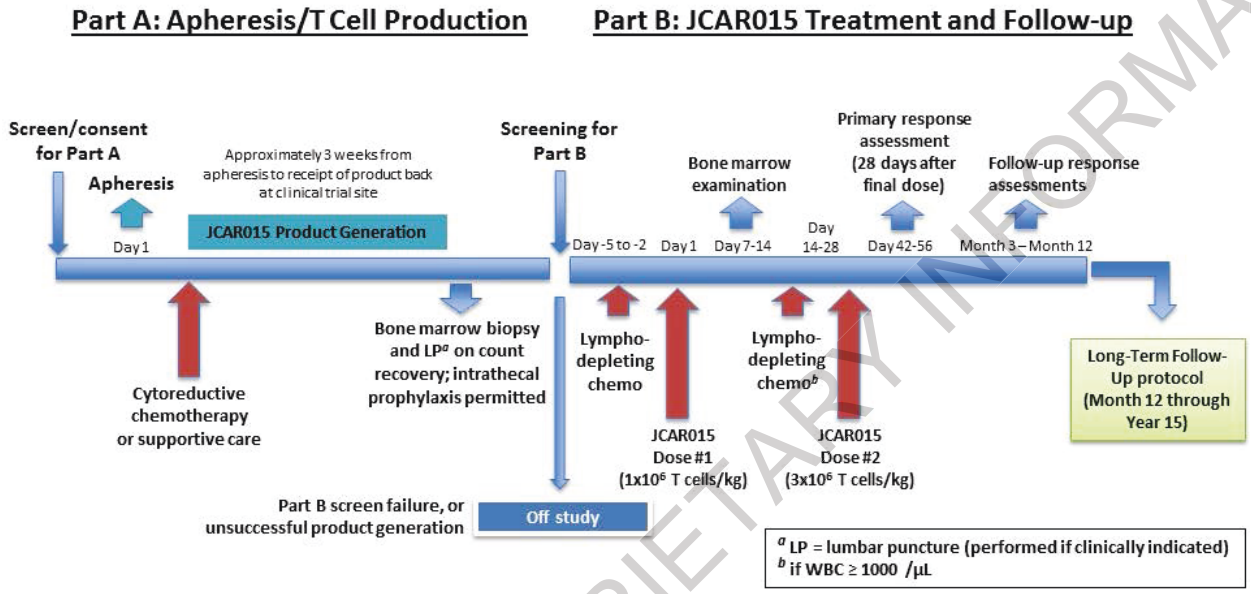
The efficacy of JCAR015 will be evaluated using the primary endpoint of ORR (CR + CRi) at 28 days after the final JCAR015 infusion (i.e., Dose #2 for subjects that complete JCAR015 treatment or Dose #1 for subjects who receive only one dose of JCAR015).

Additional efficacy assessments will occur at Months 3, 6, and 12 after the final JCAR015 infusion, or until the subject requires alternative therapy for his or her disease. Response assessment will utilize guidelines based on Cheson et al. (Cheson 2003) and National Comprehensive Cancer Network (NCCN) ALL Guidelines (National Comprehensive Cancer Network 2014) (see

Section 8.3.1). Safety, relapse, and survival will be assessed until the end of the treatment and primary follow-up phase (12 months after the final JCAR015 infusion). Post-study follow-up for survival, relapse, long-term toxicity, and viral vector safety and persistence will continue under a separate long-term follow-up (LTFU) protocol through up to 15 years after the final JCAR015 infusion as per health authority regulatory guidelines.

A schematic of the study design is presented in Figure 3.

Figure 3: Study Schematic



4.1.1 Subject Treatment Plan for Amendment 5

In response to the safety events described in Section 1.5 and following discussion with the FDA, resumption of treatment of subjects under the current protocol amendment (Amendment 5) will utilize a gated treatment plan as follows:

- For clinical trial sites that have treated at least one subject through Dose #2 as of 07 July 2016, there are no restrictions on the screening and enrollment of subjects. The original requirement that newly initiated clinical trial sites must treat one subject through Dose #2 before enrolling additional subjects continues to apply.
- For the first six subjects eligible for treatment, only one subject across all sites may be treated in any calendar week.
- After the first six subjects are treated with JCAR015 and cyclophosphamide lymphodepletion and followed for at least 14 days after Dose #1, if there is no safety signal observed, the study will move to open (i.e., ungated) treatment across all eligible sites.
- Because the three observed events of Grade 5 cerebral edema described in Section 1.5 occurred in subjects below the age of 30, gated treatment (i.e., only one subject across all sites treated within any calendar week) will continue for subjects under the age of 30 until

six subjects under the age of 30 have been treated with JCAR015 and cyclophosphamide lymphodepletion and followed for at least 14 days after Dose #1. If there is no safety signal observed in these six subjects under the age of 30, the study will move to open (i.e., ungated) treatment across all eligible sites for subjects under the age of 30.

4.1.2 Part A: Leukapheresis and Production of JCAR015 T-Cell Product

In Part A, subjects will provide informed consent, complete all screening procedures, and undergo leukapheresis to enable product generation (see Section 6.1). Leukapheresis may be performed prior to completion of screening procedures. Eligible subjects who meet all inclusion and exclusion criteria will be enrolled into the study.

Following leukapheresis and concurrent with generation of JCAR015, subjects will receive, at the Investigator's discretion, either cytoreductive chemotherapy based on the Investigator's choice of five protocol-specified regimens, and/or supportive care (e.g., blood products, hydroxyurea, 6-mercaptopurine) if the Investigator believes that the trajectory of the subject's disease progression will allow for this option. The Investigator may choose one of the following cytoreductive chemotherapy regimens (see Section 6.2 for further details regarding the use of cytoreductive chemotherapy):

- A vincristine-based regimen, such as vincristine + prednisone, POMP (Rodriguez 1973), or vincristine sulfate liposomal injection (VLSI) monotherapy (Pathak 2014)
- Cytarabine (including high-dose cytarabine) ± mitoxantrone (Larson 2012), or MEC (Amadori 1991)
- FLAG-IDA (Specchia 2005) (or FLAG alone, if further anthracycline exposure is contraindicated)
- Hyper-CVAD or mini-hyper-CVD (course A or course B) (Kantarjian 2004, Jain 2013)
- An FDA-approved tyrosine kinase inhibitor (TKI; e.g., nilotinib, bosutinib, ponatinib)

Subjects will be managed and monitored per institutional practice following administration of cytoreductive chemotherapy (see Section 6.4 for allowable supportive care measures and Section 6.5 for prohibited agents).

4.1.3 Bone Marrow Evaluations for Part B Screening

Bone marrow examinations will be performed for Part B screening upon completion of cytoreductive chemotherapy and notification of JCAR015 product availability, or upon notification of JCAR015 product availability for subjects that do not receive cytoreductive chemotherapy, as described below. Subjects must have a bone marrow examination within 10 days prior to the start of lymphodepleting chemotherapy. If more than 10 days transpire between the initial bone marrow examination conducted at Part B screening and initiation of lymphodepleting chemotherapy, the bone marrow examination must be repeated. Only those results from bone marrow examination performed within 10 days prior to initiation of lymphodepleting chemotherapy will be collected and used as baseline data for evaluation of the primary endpoint.

Subjects with hematopoietic recovery or refractory leukemia after cytoreductive chemotherapy

Subjects with signs of hematopoietic recovery or refractory leukemia (e.g., > 1% blasts in the peripheral blood) will have a bone marrow examination to assess disease status, as well as to collect specimens for biomarker evaluations, approximately 14 to 21 days after initiation of chemotherapy, coincident with notification of JCAR015 product availability.

Subjects without hematopoietic recovery or refractory leukemia after cytoreductive chemotherapy

Subjects without evidence of hematopoietic recovery or refractory leukemia at 21 days after initiation of chemotherapy will undergo a bone marrow examination at that time to assess disease status, as well as to collect specimens for biomarker evaluations.

- Subjects with extensive marrow disease that, in the Investigator's opinion, would prevent hematopoietic recovery will proceed to JCAR015 infusion in Part B and will be analyzed in Group 1.
- Subjects with an aplastic marrow or hypoplastic bone marrow ("recovery marrow") will be monitored by peripheral blood counts and repeat bone marrow examinations between 21 and 42 days after initiation of chemotherapy.
  - Subjects with evidence of hematopoietic recovery during this timeframe will undergo a repeat bone marrow examination.
    - Those with morphologic evidence of disease will proceed to treatment in Part B and will be analyzed in Group 1;
    - Subjects achieving morphologic remission (CR or CRi) will be analyzed in Group 2.
  - Subjects who continue to have a hypoplastic or aplastic marrow at 42 days after initiation of chemotherapy, where the extent of marrow involvement cannot be determined, will proceed to treatment in Part B and will be analyzed in Group 2.

Subjects who do not receive cytoreductive chemotherapy

Subjects who only receive supportive care in Part A and do not receive cytoreductive chemotherapy will have a bone marrow examination approximately 7 days following notification of JCAR015 availability to collect specimens for biomarker evaluations. Following bone marrow examination, subjects will proceed to treatment in Part B.

4.1.4 Part B: JCAR015 Treatment, Response Evaluation, and Follow-up Assessments

Subjects who are eligible for treatment in Part B will receive two IV doses of JCAR015 CAR T cells administered 14 to 28 days apart. The first JCAR015 infusion will be preceded 2 to 5 days earlier by a single dose of cyclophosphamide (1.0 to 3.0 g/m^2 IV). For subjects with a white blood cell (WBC) count ≥ 1,000/μL, the second JCAR015 infusion may be preceded 2 to 5 days earlier by a second dose of cyclophosphamide at the discretion of the Investigator (see Table 5).

Subjects will have a bone marrow examination 14 days following the first JCAR015 dose to assess in vivo JCAR015 engraftment and expansion.

Table 5: JCAR015 Treatment Schedule and Response Evaluation

	Treatment	Required for	Dose	Timing
JCAR015 Dose #1	Cyclophosphamide	All subjects	1.0-3.0 g/m^2 IV	2-5 days prior to JCAR015 Dose #1[a]
	JCAR015	All subjects	1 × 10^6 JCAR015 cells/kg[b]	Day 1[c]
Bone marrow examination (assessment of JCAR015 engraftment/ expansion)		All subjects		Day 14
JCAR015 Dose #2	Cyclophosphamide	May be given to subjects with WBC count ≥ 1000/µL at the discretion of the Investigator	1.0-3.0 g/m^2 IV	2-5 days prior to JCAR015 Dose #2[d]
	JCAR015	All subjects	3 × 10^6 JCAR015 cells/kg[b]	14-28 days after JCAR015 Dose #1[c]
Bone marrow examination (response assessment)[e]		All subjects		28 (±2) days after JCAR015 Dose #2[e]

[a] Lymphodepleting chemotherapy/JCAR015 Dose #1 may be delayed up to 12 weeks after initiation of cytoreductive chemotherapy to allow recovery from any toxicities or illnesses arising during Part A (see Section 6.3.8) or up to 8 weeks after initiation of cytoreductive chemotherapy for scheduling or logistical issues (see Section 8.2.2.1)

[b] JCAR015 dose indicates target cell dose

[c] JCAR015 may be delayed up to 7 days after completion of lymphodepleting chemotherapy to allow recovery from toxicities associated with prior lymphodepleting chemotherapy (see Section 8.2.2.3)

[d] Lymphodepleting chemotherapy/JCAR015 Dose #2 may be delayed up to 8 weeks to allow recovery from any toxicities or illnesses arising after Dose #1 (see Sections 6.3.8 and 8.2.2.5)

[e] Subjects who have not received JCAR015 Dose #2 by 28 days after Dose #1 will have a bone marrow assessment at 28 (±2) days after the first dose of JCAR015.

All subjects who receive two doses of JCAR015 will undergo a bone marrow examination 28 (±2) days after the second dose. Subjects who have not received the second dose of JCAR015 by 28 days after the first dose will undergo a bone marrow examination 28 (±2) days after the first dose. Following the 28-day bone marrow examination, all subjects will continue to have all scheduled assessments as detailed in Appendix B for Post-Infusion Monitoring Month 2 through Month 9 (visits for subjects who receive only one dose of JCAR015 will be scheduled relative to the date of the first infusion).

Following each JCAR015 infusion, subjects will undergo study-specified disease and biomarker evaluations (see Section 8.2.2 and Schedule of Events table in Appendix C). Subjects will be closely monitored for AEs, in particular CRS, neurotoxicity, tumor lysis syndrome (TLS), infusion

reactions, and other unanticipated adverse reactions. Subjects should receive appropriate supportive care, including tranfusions, filgrastim, or pegfilgrastim as per institutional or standard clinical practice. Hospitalized subjects may be discharged when they are clinically stable.

Following completion of the JCAR015 infusion(s), subjects will complete all follow-up assessments per study protocol (see Section 8.2.2 and Schedule of Events table in Appendix B). Serial sampling of blood and bone marrow will be performed to assess safety, efficacy, and cellular PK of JCAR015.

4.2 Study Duration and Duration of Subject Participation

This trial will enroll an estimated 110 subjects to ensure that a minimum of 50 subjects are included in the primary efficacy analysis set. The enrollment period is expected to take up to 24 months and the follow-up period for each subject is approximately 12 months after the final JCAR015 infusion. Thus, the total duration of the study is expected to be approximately 3 years. Long-term follow-up for survival, toxicity, and viral vector safety and persistence will continue under a separate LTFU protocol per health authority regulatory guidelines, currently up to 15 years after the last JCAR015 infusion.

The total duration of participation for subjects who complete the study will be approximately 14 months (approximately 1 month in Part A and approximately 13 months in Part B). All subjects who receive at least one JCAR015 infusion will continue to be followed under the LTFU protocol.

4.3 Stopping Rules

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the patient population being accrued and on the nature of the advanced hematologic malignancy under study. As a result, there is no specific incidence rate of SAEs that will define a stopping rule. Instead, regular systematic review of SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are related to JCAR015 will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the DSMB, the Sponsor, and the Medical Monitor. Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

4.3.1 Criteria for Pausing or Stopping the Study

The study will be paused for enrollment pending notification of the DSMB and appropriate regulatory authorities if any subject experiences any of the following events within 30 days of a JCAR015 cell product infusion:

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

  Expected toxicities include up to Grade 4 CRS, neurotoxicity (e.g., confusion, aphasia, seizures, convulsions, lethargy, and/or altered mental status), fever, hypotension, hypoxia,

TLS, and disseminated intravascular coagulation. In addition, ICU admission, the need for dialysis, and/or the need for mechanical ventilation are also expected. The expected toxicities may also result in secondary toxicities of Grade 4 renal toxicity, hepatic toxicity, or other organ involvement.

- Death related to JCAR015 therapy

The study will be terminated for the following reasons:

- Any subject develops uncontrolled JCAR015 proliferation that is unresponsive to treatment
- Any subject develops detectable replication-competent retrovirus (RCR) during the study
- The Sponsor, IRB/IEC, or DSMB decides that subject safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of JCAR015 in this indication or the development of JCAR015 for all indications

4.3.2 Safety Monitoring Boundaries

In addition to the aforementioned criteria, safety monitoring boundaries based on a Bayesian framework (Thall 1994, Yao 2013) have been implemented to help detect safety signals that may occur during the course of the study. The boundaries are based on the cumulative number of subjects experiencing either of the following events within 30 days of a JCAR015 cell product infusion:

- A Grade 3 JCAR015-related treatment-emergent AESI that is unmanageable or fails to resolve to Grade 2 or better after 21 days
- A Grade 4 JCAR015-related treatment-emergent AESI that is unmanageable or fails to resolve to Grade 3 or better after 7 days

If the safety boundaries are crossed, enrollment will be paused and an ad hoc DSMB meeting will be held to review the data. The study will remain paused for enrollment pending the DSMB's recommendations. Details regarding the Bayesian framework and the safety monitoring boundaries are included in the statistical analysis plan.

4.4 Removal of Subjects from Study

At the time of consent for the study, subjects will be advised that they are free to withdraw from the study at any time for any reason; however, subjects will be encouraged to continue all study evaluations scheduled through the End-of-Study (EOS) visit at 12 months after the final dose of JCAR015. Juno Therapeutics, Inc. must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and the case report form (CRF).

Subjects who are withdrawn prior to receiving JCAR015 will be removed from the study.

4.4.1 Criteria for Subject Withdrawal from Further Study Treatment

Subjects who receive the first JCAR015 infusion and are subsequently withdrawn from further study treatment (e.g., due to toxicity) will not be withdrawn from the study. They will remain on study and continue to have all scheduled safety and efficacy evaluations through the EOS visit at 12 months after the JCAR015 infusion per the Schedule of Events table (Appendix B). In addition, these subjects will be followed for up to 15 years after the JCAR015 infusion under the LTFU protocol (see Section 8.2.8).

Subjects may be withdrawn from further study treatment for any of the following reasons:

- Investigator decision
- Subject decision
- The subject experiences an SAE or medically important AE that would preclude further treatment with JCAR015
- The subject requires medical treatment excluded by the protocol
- The subject experiences an increase in disease activity that requires additional or different therapy
- Inability to receive lymphodepleting chemotherapy due to elevated serum creatinine (see Section 6.3.9)

Withdrawal from study treatment does not necessitate withdrawal from the study.

4.4.2 Criteria for Subject Withdrawal from Study

Subjects may voluntarily withdraw from the study at any time. In addition, subjects will be withdrawn from the study if any of the following occurs:

- Failure to generate a JCAR015 dose that meets the required quality control (QC) and release criteria as defined by Juno manufacturing
- The subject is noncompliant with study requirements or procedures that, in the opinion of the Investigator or Sponsor, prevents the safe administration of JCAR015
- Subject withdrawal of consent
- Study termination by the Sponsor, an IRB/IEC, a regulatory authority such as the FDA, or based on a determination of the DSMB
- Lost to follow-up (should be recorded as such in the case report form [CRF])
- Significant and rapid progression of disease that requires alternative medical or surgical intervention prior to the EOS visit
- Subject undergoes hematopoietic stem cell transplantation
- Death

Subjects who are withdrawn from the study because of prolonged illness during Part A or failure to generate a JCAR015 dose that meets the required QC and release criteria may re-enroll in the study at a later time provided that the subject meets all eligibility criteria. Subjects who re-enroll will undergo another leukapheresis procedure for generation of JCAR015 T cell product. A second leukapheresis is not required for subjects who re-enroll and have an available JCAR015 cell

product that met the release criteria. Subjects who have withdrawn from the study after receiving at least one dose of JCAR015 and subjects who relapse following treatment with JCAR015 may not re-enroll in the study.

4.4.3 Data Collected for Subjects Withdrawn from Study

If a subject elects to withdraw prematurely from the study during Part A, JCAR015 will not be administered, and an EOS visit should be conducted within 30 days (see Section 8.2.5). If a subject elects to withdraw prematurely from the study during Part B, study staff should make every effort to complete the full panel of assessments scheduled for the EOS visit.

All subjects who receive at least one dose of JCAR015 and are prematurely withdrawn from study should be asked to participate in the LTFU protocol at the time of withdrawal. Subjects who do not agree to participate in the LTFU protocol or who are lost to follow-up will be followed for survival through public record.

4.4.4 Criteria for Termination of the Study

The study can be terminated at any time by the Sponsor, the FDA, the DSMB, or an IRB/IEC for any reason. 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 informing IRBs/IECs and any other regulatory committee (as applicable) of the early termination of the trial.

4.4.5 Replacement of Study Subjects

Subjects who withdraw prematurely from the study will not be replaced; however, subjects will continue to be accrued until a minimum of 50 subjects who meet criteria for inclusion in the primary efficacy analysis set (see Section 10.2.4) have been enrolled.

5 STUDY POPULATION

5.1 Part A

Subjects must meet all of the Part A criteria to be enrolled into this study:

5.1.1 Inclusion Criteria (Part A)

1. Age ≥ 18 years at the time of consent
2. Signed written informed consent obtained prior to any Part A study procedures
3. Diagnosis of B-cell ALL by flow cytometry
4. Relapsed or refractory disease, defined as:
   a. First or greater bone marrow relapse from CR, OR
   b. Any bone marrow relapse after allogeneic HSCT; subjects must be at least 100 days from HSCT (i.e., Day 0, receipt of hematopoietic stem cells) at the time of screening and off immunosuppressant medication for at least 1 month at the time of screening (with the exception of low-dose steroids [≤ 20 mg prednisone or equivalent]), and have no active GVHD, OR
   c. Refractory ALL, defined by not having achieved a CR or CRi after two attempts at remission induction using standard regimens, OR
   d. Ph+ B-cell ALL if subjects are intolerant to or ineligible for TKI therapy, OR have progressed after at least one line of TKI therapy
5. Bone marrow with morphological evidence of disease (≥ 5% blasts by morphology)
6. Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) from a sample obtained from the current relapse within 2 months of screening
7. Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2 at the time of screening
8. Adequate organ function, defined as:
   a. Serum creatinine ≤ 1.5 × age-adjusted upper limit of normal (ULN) OR calculated creatinine clearance (Cockcroft and Gault; see Appendix E) > 30 mL/min/1.73 m^2
   b. Alanine aminotransferase (ALT) ≤ 5 × ULN (or ≤ 8 × ULN for subjects with leukemic infiltration of the liver) and direct bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with leukemic infiltration of the liver)
   c. Adequate pulmonary function, defined as ≤ Grade 1 dyspnea and SaO_2 ≥ 92% on room air
   d. Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multiple uptake gated acquisition (MUGA) performed within 1 month of enrollment
9. Adequate central or peripheral vascular access for leukapheresis procedure. If a subject requires central venous catheter (CVC) placement in order to perform leukapheresis, a

consultation indicating subject eligibility for CVC placement is sufficient to allow enrollment on the study while the subject awaits CVC placement.

10. Women of reproductive potential (defined as all women physiologically capable of becoming pregnant) must agree to use highly effective methods of contraception during the entire study period (Part A through 12 months after the final JCAR015 infusion) (see Section 5.3). Women of reproductive potential must have a negative serum beta human chorionic gonadotropin (ß-hCG) pregnancy test result within 7 days prior to the first dose of cytoreductive chemotherapy.
11. Males who have partners of childbearing potential must agree to use an effective barrier contraceptive method during the entire study period (Part A through 12 months after the final JCAR015 infusion).

5.1.2 Exclusion Criteria (Part A)

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

1. Isolated extramedullary disease relapse
2. Concomitant genetic syndrome such as Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known bone marrow failure syndrome
3. Burkitt's lymphoma/leukemia or chronic myelogenous leukemia (CML) lymphoid blast crisis (p210 BCR-ABL+)
4. Prior malignancy, unless treated with curative intent and with no evidence of active disease present for > 5 years before screening, with the following exceptions:
    a. Subjects with Stage I breast cancer that has been completely and successfully treated, requiring no therapy or only anti-hormonal therapy
    b. Subjects with T1N0M0 or T2N0M0 colorectal cancer who have been completely and successfully resected and who are disease-free for > 2 years prior to screening
    c. Subjects with indolent prostate cancer, defined as clinical stage T1 or T2a, Gleason score ≤ 6, and prostate-specific antigen (PSA) < 10 ng/mL, requiring no therapy or only anti-hormonal therapy
    d. Subjects with a history of basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the cervix, fully resected, and with no evidence of active disease
5. Treatment with any prior gene therapy product
6. Active hepatitis B, active hepatitis C, or any human immunodeficiency virus (HIV) infection at the time of screening
7. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) at the time of screening
8. Presence of Grade II-IV (Glucksberg) or B-D (IBMTR) acute or extensive chronic GVHD at the time of screening

9. Active CNS involvement by malignancy, defined as CNS-3 per NCCN guidelines. Subjects with a history of CNS disease that has been effectively treated (defined as one documented negative CSF evaluation within 1 month prior to screening) will be eligible.
10. History of any one of the following cardiovascular conditions within the past 6 months: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease
11. History or presence of clinically relevant CNS pathology such as epilepsy, generalized seizure disorder, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
12. Participation in an investigational research study using an investigational agent within 30 days of screening, with the exception of investigational anti-infective agents (e.g., antibacterial, antifungal, antiviral)
13. History of treatment with a murine-derived biological product (unless subject has been shown to be negative for human anti-mouse antibodies [HAMA] prior to or during screening). Prior use of blinatumomab is permitted (provided there is evidence of CD19 expression per Inclusion Criterion #6). Chimeric biological products (e.g., rituximab) are not considered murine for the purpose of this protocol.
14. Pregnant or nursing (lactating) women
15. Use of prohibited medications (see Section 6.5 for full details):
    a. Steroids: Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) are prohibited within 7 days prior to leukapheresis. Physiologic replacement dosing of steroids (≤ 12 mg/m^2/day hydrocortisone or equivalent [≤ 3 mg/m^2/day prednisone or ≤ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids and intrathecal steroids for CNS relapse prophylaxis are permitted.
    b. Allogeneic cellular therapy: Donor lymphocyte infusions (DLI) are prohibited within 4 weeks prior to leukapheresis
    c. GVHD therapies: Any drug used for GVHD within 4 weeks prior to leukapheresis, e.g., calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate mofetil, rapamycin, thalidomide, immunosuppressive antibodies (such as anti-CD20 [rituximab], anti-TNFα, anti-IL-6, or anti-IL-6R)
    d. Chemotherapies: Salvage chemotherapy (e.g., cytosine arabinoside > 100 mg/m^2/day, anthracyclines, and cyclophosphamide) must be stopped at least 1 week prior to leukapheresis
16. Treatment with alemtuzumab within 6 months prior to leukapheresis, or treatment with clofarabine or cladribine within 3 months prior to leukapheresis
17. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, as judged by the Investigator; or subject unwillingness or inability to follow the procedures required in the protocol

5.2 Part B

Study investigators must ensure that only subjects who meet all inclusion and exclusion criteria are enrolled in Part B and treated with JCAR015. Assessments conducted for evaluation of eligibility in Part A may not be used to evaluate eligibility for Part B.

5.2.1 Inclusion Criteria (Part B)

1. Completion of Part A and successful generation of a JCAR015 cell product
2. Results from bone marrow examination following Part A:
   a. Group 1: Morphological evidence of disease (≥ 5% blasts by morphology)
   b. Group 2: Morphologic complete remission (bone marrow with < 5% blasts) with or without blood count recovery (CR or CRi) or a hypoplastic, aplastic, or "recovery" marrow at Day 42 of Part A
3. ECOG performance status between 0 and 2
4. Adequate organ function, defined as:
   a. Serum creatinine ≤ 1.5 × age-adjusted ULN OR calculated creatinine clearance (Cockcroft and Gault; see Appendix E) > 30 mL/min/1.73 m^2
   b. ALT ≤ 5 × ULN (or ≤ 8 × ULN for subjects with leukemic infiltration of the liver) and direct bilirubin < 2.0 mg/dL (or < 3.0 mg/dL for subjects with leukemic infiltration of the liver)
   c. Adequate pulmonary function, defined as ≤ Grade 1 dyspnea and SaO_2 ≥ 92% on room air
5. Women of reproductive potential must have a negative serum or urine pregnancy test

5.2.2 Exclusion Criteria (Part B)

Subjects must not meet any of the following criteria prior to Part B to be considered eligible:

1. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)
2. Presence of Grade II-IV (Glucksberg) or B-D (IBMTR) acute or extensive chronic GVHD
3. Use of prohibited medications (see Section 6.5)

5.3 Childbearing Potential and Contraception Requirements

Any female subject who does not meet at least one of the following criteria will be considered to have reproductive potential:

- Post-menopausal for at least 12 consecutive months (i.e., no menses), or
- Undergone a sterilization procedure (hysterectomy, salpingotomy, or bilateral oophorectomy; tubal ligation is *not* considered a sterilization procedure)

Female study participants of reproductive potential must have a negative serum pregnancy test at the Part A screening evaluation, and a negative serum or urine pregnancy test at the Part B screening evaluation.

Female subjects with reproductive potential who are not sexually abstinent and male subjects who are sexually active with females of reproductive potential must agree to use one of the following methods of contraception for the duration of the study (from Part A screening through 12 months after the final JCAR015 infusion):

- Condom with spermicidal agent
- Diaphragm or cervical cap with spermicidal agent
- Intrauterine device
- Hormonal contraceptives in combination with either a condom, diaphragm, or cervical cap

6 STUDY TREATMENTS

6.1 Leukapheresis (Part A)

Following enrollment on the study, a standard leukapheresis collection will be performed on each subject to obtain PBMCs as specified in the Juno Therapeutics Clinical MNC Collection Protocol. Collections will be performed per a standard procedure at a cell collection center that has been qualified by Juno Therapeutics, Inc. Collections must be performed on equipment approved by the FDA for the collection of mononuclear cells. Autologous plasma will also be added to the product to ensure stability during transportation. The leukapheresis product should be handled according to local institutional policies and procedures, in accordance with applicable regulations (including, but not limited to, 21 CFR §1271.145), and Occupational Safety and Health Administration (OSHA) Universal Precautions. When the collection is complete, the product will be packaged and shipped to the manufacturing site in a shipping container designed to maintain a temperature of 2° to 8°C. Should a technical issue arise during the procedure or in the immediate processing of the product such that it cannot be used for JCAR015 production, a second collection procedure may be needed.

Re-enrolled subjects who have an available JCAR015 cell product that met release criteria are not required to undergo a second leukapheresis.

6.2 Cytoreductive Chemotherapy (Part A)

Following leukapheresis, during the period of JCAR015 manufacture, subjects may receive chemotherapy for the purpose of disease control and cytoreduction. It is estimated that it will require approximately 3 weeks from receipt of the leukapheresis product at the manufacturing site to successfully generate JCAR015 product. If, in the opinion of the Investigator, the proliferative rate of the subject's disease is such that supportive care alone (e.g., hydroxyurea, blood products, 6-mercaptopurine) will provide sufficient disease control during this timeframe, the Investigator may choose to forego treatment with cytoreductive chemotherapy.

The Investigator may choose from the following regimens based on the subject's prior medical and chemotherapeutic history, prior adverse reactions to chemotherapy, disease burden, and other subject-specific factors:

- A vincristine-based regimen, such as vincristine + prednisone, POMP (Rodriguez 1973), or vincristine sulfate liposomal injection (VLSI) monotherapy (Pathak 2014)
- Cytarabine (including high-dose cytarabine) ± mitoxantrone (Larson 2012), or MEC (Amadori 1991)
- FLAG-IDA (Specchia 2005) (or FLAG alone, if further anthracycline exposure is contraindicated)
- Hyper-CVAD or mini-hyper-CVD (course A or course B) (Kantarjian 2004, Jain 2013)
- An FDA-approved TKI (e.g., nilotinib, bosutinib, ponatinib)

For subjects receiving prednisone as part of cytoreductive chemotherapy, it should be noted that therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) are prohibited within 72 hours prior to JCAR015 infusion.

Choice of chemotherapy should be documented in the subject's medical record and the CRF. Each regimen is of a different duration, so the start and end dates of chemotherapy may vary. These chemotherapy regimens are not investigational and may be given by a subject's local oncologist within the specified time frame.

6.3 Investigational Treatment: JCAR015

6.3.1 Description of Investigational Product

JCAR015 cell product consists of autologous CD3+, CD4+ and CD8+ T cells that are genetically modified via gammaretroviral vector transduction to express the 1928z CD19-specific CAR under the control of the Mo-MuLV long terminal repeat (LTR) (Riviere 1995). The CAR consists of a CD19-specific scFv, derived from the murine monoclonal antibody SJ25C1, fused to the transmembrane and cytoplasmic signaling domains of CD28 and the cytoplasmic signaling domain of the CD3ζ chain.

CD4+ and CD8+ T cells from a subject's leukapheresis unit are isolated ex vivo using commercially available magnetic bead-antibody reagents. The T cells are subsequently activated with a commercially available T cell activation reagent and then transduced with the CAR gammaretroviral vector. The residual non-integrated vector is washed away. JCAR015 cells are expanded ex vivo to a therapeutic dose in a controlled bioreactor. At the end of the culture, the JCAR015 cells are washed and formulated in a mixture of Plasma-Lyte A and a proprietary cryopreservation media. The final formulation contains approximately 7.5% (v/v) dimethyl sulfoxide (DMSO).

6.3.2 Product Tracking

The identity of the investigational product will be checked and verified at each critical step of cell processing. Procedures will be in place to address product tracking requirements and will encompass all process steps including collection of the leukapheresis product, receipt of the leukapheresis product, JCAR015 manufacturing and testing, in-process labeling, and JCAR015 labeling and packaging for shipment.

6.3.3 Product Packaging and Labeling

Each JCAR015 infusion bag label will include the following information:

- Product code
- Subject name (first and last)
- Subject date of birth
- Unique Juno-assigned subject study number
- Unique treatment/lot identifier (Juno Order Identification Number [JOIN])

These same identifiers are maintained from leukapheresis collection throughout the manufacturing process and are used on the final JCAR015 cell product. The final JCAR015 cell product is provided frozen and packaged in ethylene vinyl acetate cryobags, each containing approximately 1×10^6 CAR^+ $CD3^+$ cells/kg subject weight in an approximate volume of 60 mL. The cryobags are

provided to the study site per the dosing regimen specified in Section 6.3.7. The final product infusion bag will be labeled as listed above for ease of identification of product/subject identity. These unique identifiers should be verified per the Chain of Identity procedures listed in the JCAR015 Product Administration Manual.

Prior to the JCAR015 infusion, two trained individuals will verify all unique identifier information in the presence of the subject to confirm that the information is correctly matched to the subject.

6.3.4 Cell Product Supply and Storage

JCAR015 Dose #1 and Dose #2 will be shipped separately. The JCAR015 cell product will arrive frozen in an insulated shipping container designed to maintain a temperature of -60°C or below for at least 48 hours. The product should be stored in the unopened shipping container until the time of thaw prior to administration.

Detailed instructions on the storage, handling, and preparation of JCAR015 cell product will be provided in the JCAR015 Product Administration Manual.

6.3.5 Accountability Procedures

An inventory must be performed and a product receipt log filled out and signed by the person accepting the shipment of JCAR015 cell product.

6.3.6 Drug Disposal and Destruction

Any used or unused product and all unused infusion supplies must be disposed of in accordance with the institution's policy and 29 CFR §1910.1030 (Bloodborne Pathogens Standard). Source document verification will be performed and reconciled against the documentation of quantity shipped, received, dispensed, and disposed.

6.3.7 Dosing Regimen

A course of therapy will consist of two doses of JCAR015 cell product. The first dose will consist of a single infusion of 1×10^6 JCAR015 cells/kg (target cell dose) and will be preceded 2 to 5 days earlier by lymphodepleting chemotherapy (see Section 6.3.9 for lymphodepleting chemotherapy regimen). The second dose will consist of a single infusion of 3×10^6 JCAR015 cells/kg (target cell dose) and will be scheduled to occur 14 to 28 days after the first JCAR015 infusion. Subjects whose WBC count $\geq$ 1000/µL may receive a second course of lymphodepleting chemotherapy 2 to 5 days prior to the scheduled second infusion at the discretion of the Investigator. For subjects whose WBC count is < 1000/µL, the second course of lymphodepleting chemotherapy is not required.

6.3.8 Criteria for JCAR015 Treatment

The minimum acceptable dose for manufacturing release is 1×10^6 JCAR015 cells/kg. Subjects whose total manufactured JCAR015 dose is less than the release criteria for the 1×10^6 JCAR015 cells/kg dose level will be removed from study. Subjects with a total manufactured cell dose that is greater than the release criteria for the 1×10^6 JCAR015 cells/kg dose level but less than the total target dose of 4×10^6 JCAR015 cells/kg will receive their cell infusion(s). Subjects with

morphologic disease at the time of JCAR015 infusion who have a manufactured cell dose that meets release criteria but is less than the target dose will be included in Group 1 and considered evaluable for the primary endpoint.

For subjects experiencing toxicities or other illnesses during Part A, lymphodepleting chemotherapy and JCAR015 infusion may be delayed for up to 12 weeks until these toxicities or other illnesses have resolved so that the subject meets Part B inclusion/exclusion criteria. Delays of up to 8 weeks are allowed for scheduling or logistical issues. If a subject's first JCAR015 infusion is delayed > 12 weeks from the start of cytoreductive chemotherapy, the subject should be withdrawn from the study. Subjects who, in the judgment of the Investigator, are clinically unfit to receive JCAR015 or who are unlikely to be clinically fit to receive JCAR015 within 12 weeks after the start of cytoreductive chemotherapy should also be withdrawn from the study.

For subjects meeting the criteria for severe CRS (sCRS) after the first infusion of JCAR015, the second JCAR015 infusion may be delayed until CRS has resolved to Grade 2 or less (see Section 7.1). For subjects with other Grade 3 or greater AE(s) or SAE(s) after the first infusion of JCAR015, the second JCAR015 infusion may be delayed until the AE(s) or SAE(s) have resolved to Grade 2 or less. The second JCAR015 infusion may be delayed up to 8 weeks from the first JCAR015 infusion to allow for recovery from toxicity or other illnesses arising after the first JCAR015 infusion. If a subject's second JCAR015 infusion is delayed for more than 8 weeks from the first JCAR015 infusion, the subject should be withdrawn from further study treatment and follow the schedule for post-Dose #1 monitoring (see Appendix B). Subjects who have not received the second dose by Day 28 should complete all Post Dose #1 Day 28 assessments, including bone marrow evaluation, while waiting to recover from CRS or other toxicities.

6.3.9 Lymphodepleting Chemotherapy

Subjects will receive lymphodepletion with a single dose of cyclophosphamide 1.0-3.0 g/m^2 IV (Brentjens 2013) 2 to 5 days prior to JCAR015 administration. The highest dose of cyclophosphamide within the dosing range should be used when possible (e.g., 3.0 g/m^2), particularly for subjects with a high disease burden. The dose of cyclophosphamide in the lymphodepleting chemotherapy regimen can be reduced, based on the Investigator's assessment, in order to take into account the subject's underlying organ function (i.e., renal, cardiac) and hematopoietic capacity.

Serum creatinine will be measured the day of lymphodepleting chemotherapy treatment, and chemotherapy should be withheld if serum creatinine > 2 mg/dL. The subject will be removed from study treatment if serum creatinine remains > 2 mg/dL for more than 14 days despite medical management (intravenous fluids and other appropriate medications), thereby preventing the safe administration of cyclophosphamide.

For the second dose of JCAR015, lymphodepleting chemotherapy should be withheld if the subject's WBC count is < 1000/µL.

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.

6.3.10 JCAR015 Premedication

Side effects accompanying autologous T cell infusion may include transient fever, chills, and/or nausea (Davila 2014, Lee 2014, Maude 2014). Subjects should be pre-medicated with 650 mg acetaminophen PO or 25 to 50 mg diphenhydramine hydrochloride (PO or IV) or both (at the discretion of the Investigator) 30 to 60 minutes prior to each infusion of JCAR015. These medications may be repeated every 6 hours as needed based on Investigator assessment of symptoms.

6.3.11 JCAR015 Preparation and Cell Thawing

The JCAR015 shipping container must be opened and thaw commenced prior to the packaging expiration date and time indicated on the outer cardboard shipping box. Before use, it should be verified that the packaging expiration date and time indicated on the outer cardboard shipping box has not been exceeded.

The product bag(s) should be thawed one at a time and inspected for signs of leakage or external damage prior to infusion. The product is thawed at room temperature (the use of water bath or any other thawing method is not allowed); thaw is considered complete when no visible ice crystals can be observed in the product bag (approximately 30 minutes at 70°F/21°C). The bag may be gently massaged to facilitate thawing, but should not be shaken or aggressively handled.

Before infusion, it should be confirmed that the subject's identity matches the subject identifiers on the infusion bag(s). Infusion should begin as soon as possible upon thaw because the product formulation currently includes the cryoprotectant DMSO, which can impact cell viability with prolonged exposure at room temperature. If complications arise during infusion, the product infusion may be delayed up to 3 hours after the start of the thawing procedure. **If a thawed cryobag containing JCAR015 product has been outside of the shipping container at room temperature for longer than 3 hours, the product should be withheld or the infusion should be discontinued.**

6.3.12 JCAR015 Administration

No JCAR015 cell product is administered during Part A of the protocol.

Infusions of JCAR015 should only be administered by qualified and trained study staff using standard clinical practice for immunocompromised patients in a setting equipped for the safe administration of biological or cellular products (additional details will be provided in the JCAR015 Product Administration Manual). Subjects with morphologic evidence of leukemia in the bone marrow at the time of JCAR015 infusion are at increased risk for sCRS and should be considered for admission to the hospital for frequent monitoring of vital signs and neurologic status. Frequent monitoring of vital signs and neurologic status is important in order to promptly diagnose, treat, and successfully manage the manifestations of sCRS (see Section 7.1 for details).

JCAR015 cell product is supplied in sealed, subject-specific CS250 OriGen infusion bags; the entire volume of the bag should be infused. The number of bags supplied will depend on the number of JCAR015 cells generated and the cell dose to be delivered. Dose #1 will be supplied in one infusion bag. Dose #2 will be supplied as one, two, or three infusion bags, depending on the manufactured cell dose and concentration. For any given dose, all bags should be infused. Each

bag contains approximately 60 mL of JCAR015 T cells in suspension and will be administered by gravity via IV infusion using latex-free IV tubing over approximately 30 minutes, preferably through a central line. Use of an infusion pump is not recommended. **A leukoreduction or cell filter must NOT be used for infusion of the JCAR015 cell product. IMPORTANT: Infusion of each bag of JCAR015 cell product must be completed within 3 hours of removal from the shipping container**. The same administration set may be used to transfuse more than one bag of JCAR015 cells without interruption. The tubing set should contain a Y-arm supplement to allow the infusion circuit to be flushed with 0.9% Sodium Chloride for Injection after the infusion(s) is completed. This will allow for any remaining product left behind in the bag to be recovered and infused. IV fluids should be held during JCAR015 infusion.

All infusion supplies, including bags and tubing, must be destroyed according to the site's institutional policy and 29 CFR §1910.1030 (Bloodborne Pathogens Standard).

The subject must be continuously monitored during the infusion. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured within 15 minutes prior to, during, and within 15 minutes after the infusion, and then every 15 minutes thereafter for the first hour, and hourly for the next 3 hours. If the subject's vital signs are not stable 4 hours following JCAR015 infusion, vital signs should be monitored as clinically indicated until stable.

6.3.13 Acute Infusion Reactions

Acute infusion reactions such as chills, fatigue, fever, nausea, and joint ache may occur with autologous T cell products such as JCAR015. In addition, acute infusion reactions may occur due to excipients or to the cryoprotectant (DMSO) used to formulate JCAR015.

To minimize potential acute infusion reactions such as chills and/or fever, subjects should be pre-medicated with acetaminophen PO or an antihistamine such as diphenhydramine (PO or IV) or both (at the discretion of the Investigator) approximately 30 to 60 minutes prior to administration of JCAR015 (see Section 6.3.10). Acetaminophen and diphenhydramine may be repeated every 6 hours as needed. A course of non-steroidal anti-inflammatory medication may be given if subjects continue to have fever that is not relieved by acetaminophen.

If a subject develops toxicity other than fever within 24 hours after the JCAR015 infusion that is attributable to JCAR015, subjects will be evaluated by the Investigator. Guidelines for treatment of acute T cell infusion reactions are provided in Section 7.5. Subjects who are neutropenic at the time of JCAR015 infusion and who develop a fever should have blood cultures drawn and should be evaluated for infection and managed per institutional guidelines for febrile neutropenia.

In the event that a subject develops symptoms of systemic infection (i.e., fever, rigors, and/or hypotension) following JCAR015 infusion, blood cultures should be obtained and medical management initiated. The diagnosis of acute infusion reaction, neutropenic fever, or early CRS should be considered. Subjects should be evaluated and managed accordingly. If a contaminated JCAR015 cell product is suspected, the Sponsor should be contacted immediately so that the retained cell product sample can be retested for sterility at the manufacturing facility.

Subjects should not receive systemic corticosteroids (> 20 mg/day prednisone or equivalent) at any time during Part B, except for the treatment of Grade 2 or higher CRS. High-dose steroids

(> 2 mg/kg/day prednisone or equivalent) should not be used except in the case of life-threatening sCRS (see Section 7.1), as these agents may have an adverse effect on JCAR015 in vivo expansion and cell function.

As noted above, JCAR015 is a cryopreserved autologous cell product containing 7.5% DMSO; subjects may notice a garlic-like taste and odor. Other side effects associated with DMSO include tachycardia, bradycardia, hypertension, hypotension, chest tightness, dyspnea, pulmonary edema, abdominal cramping, diarrhea, shivering, and restlessness. Symptoms and/or AEs associated with DMSO should be managed per institutional guidelines or procedures for the infusion of autologous cell products.

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 standard (e.g., treatment with allopurinol or rasburicase, as well as adequate hydration).

Using routine complete blood counts (CBCs) as a guide, the use of red blood cells and platelet transfusions, and/or colony-stimulating factors per institutional or clinical standard is permitted. Efforts should be made to keep the hemoglobin > 8.0 g/dL and platelets > 10,000/mm^3.

Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the Investigator. Intrathecal hydrocortisone may be administered as part of intrathecal prophylactic treatment.

Subjects should be monitored for infection, cardiotoxicity, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and secondary malignancies resulting from chemotherapy treatments and managed appropriately as needed per institutional or clinical standard. The use of prophylactic or empiric anti-infective agents (e.g., trimethoprim/sulfmethoxazole for Pneumocystis jiroveci pneumonia [PCP] prophylaxis, broad spectrum antibiotics, antifungals, or antiviral agents for febrile neutropenia) per institutional standard is permitted.

Supportive care for the management of CRS is detailed in Section 7.1.

6.5 Prohibited Medications

The following medications are prohibited during the indicated timeframes:

- Steroids: Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) are prohibited within 7 days prior to leukapheresis and within 72 hours of scheduled JCAR015 infusion. Physiologic replacement dosing of steroids (≤ 12 mg/m^2/day hydrocortisone or equivalent [≤ 3mg/m^2/day prednisone or ≤ 0.45 mg/m^2/day dexamethasone]) is allowed. Topical steroids and intrathecal steroids for CNS relapse prophylaxis are permitted.
- Allogeneic cellular therapy: Donor lymphocyte infusions are prohibited within 4 weeks prior to leukapheresis.
- GVHD therapies: Any drug used for GVHD within 4 weeks prior to leukapheresis, e.g., calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate mofetil,

rapamycin, thalidomide, immunosuppressive antibodies (such as anti-CD20 [rituximab], anti-TNF, anti-IL-6, or anti-IL-6R).

- Chemotherapies:
  - Salvage chemotherapy (e.g., cytosine arabinoside > 100 mg/m^2/day, anthracyclines, and cyclophosphamide) must be stopped at least 1 week prior to leukapheresis.
  - The following drugs must be stopped at least 1 week prior to scheduled JCAR015 infusion and should not be administered concomitantly or following lymphodepleting chemotherapy: vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate < 25 mg/m^2, cytosine arabinoside < 10 mg/m^2/day, asparaginase.
  - Hydroxyurea is allowed provided the dose has been stable for at least 2 weeks prior to starting leukapheresis. Hydroxyurea must be discontinued at least 24 hours prior to the start of the first dose of cytoreductive therapy in Part A but may be given within 48 hours prior to start of lymphodepleting chemotherapy in Part B.

In addition, subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

7 POTENTIAL RISKS AND MANAGEMENT OF TREATMENT TOXICITIES

7.1 Cytokine Release Syndrome

Administration of CAR T cells, such as JCAR015, is associated with CRS, characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, and neurologic abnormalities (e.g., altered mental status, confusion, aphasia, altered level of consciousness, myoclonus, and seizures or seizure-like activity) (refer to the JCAR015 Investigator Brochure for a summary of expected neurotoxicity). Symptoms of CRS are thought to be the result of increased levels of serum cytokines including IL-6, IFNγ, and TNFα.

Severe and life-threatening toxicities may arise with CRS (i.e., sCRS), including cardiac toxicity, respiratory distress, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (Lee 2014). In these situations, ICU management, including treatment with tocilizumab, steroids, vasopressors, antiepileptics, antipyretics, and/or mechanical ventilation, may be warranted. Because CRS is a direct outcome of the intended pharmacologic action of CAR T cells, agents administered to reverse cytokine release, such as prolonged dosing with high-dose lymphotoxic steroids, may also abrogate therapeutic activity (Brentjens 2011, Davila 2014). Thus, for first-line management of Grade 2 CRS in subjects who are not at risk of life-threatening complications, it is important to consider therapies to manage CRS and cytokine-related toxicities that maintain the activity and efficacy of JCAR015. In this regard, administration of lower doses of corticosteroids (e.g., 10 mg dexamethasone IV every 12-24 hours) and/or tocilizumab, an IL-6 receptor-blocking antibody, has demonstrated resolution of sCRS symptoms without reducing blood levels of CAR T cells and should be considered for first-line management of sCRS for subjects who are not at risk for life-threatening complications (Davila 2014, Turtle 2016).

CRS symptoms typically appear within 14 days following administration of CAR T cells and may be severe or life-threatening (Lee 2014). The frequency of CRS and the probability of developing severe CRS is higher in subjects with morphologic evidence of disease (≥ 5% blasts in the bone marrow) at the time of JCAR015 infusion. CRS can start as early as 24 hours following JCAR015 infusion and can progress rapidly. Thus, vigilance in monitoring is critical. Development of high fever (greater than 39°C) and/or symptoms of CRS (e.g., hypotension or neurologic symptoms) within 96 hours after JCAR015 infusion may be indicative of early rapid expansion of JCAR015 and may require immediate treatment with tocilizumab and/or steroids.

Davila et al. at Memorial Sloan Kettering Cancer Center (MSKCC) have developed an initial set of CRS criteria that appear to correlate with the onset of CRS to predict which patients are more likely to be at risk for developing sCRS (Davila 2014). First, sCRS is typically associated with onset of fever approximately 24 hours after CAR T cell infusion that persists for several days. Second, all patients with sCRS exhibited at least one of the following symptoms: hypoxia, hypotension, or neurologic changes. Finally, patients with sCRS were noted to have elevated serum levels of inflammatory cytokines. Analysis of serum cytokines from 16 patients enrolled in Study 09-114 identified a set of seven cytokines (IFNγ, IL-5, IL-6, IL-10, Flt-3L, fractalkine, and GM-CSF) whose treatment-induced elevation appears to correlate well with both pretreatment tumor burden and sCRS symptoms (a correlation between tumor burden and magnitude of cytokine

response was previously noted (Sadelain 2013)). Patients who required intensive medical intervention for sCRS had an approximately 75-fold increase over pretreatment baseline in two of the seven cytokines identified.

Based on these observations, the group at MSKCC proposed the following diagnostic criteria for diagnosing sCRS:

- Fevers (> 38 ºC) for at least 3 days
- Two cytokine maximum changes of at least 75-fold or one cytokine maximum change of at least 250-fold
- At least one of the following:
  - One or more clinical signs of toxicity such as hypotension (requiring ≥ one intravenous vasopressor)
  - Hypoxia (pO_2 < 90%)
  - Neurologic disorders (including mental status changes, obtundation, and seizures)

Because routine cytokine level measurement is typically not available in clinical laboratories, changes in CRP were studied in patients with CRS. Elevated CRP levels were found to be a reliable indicator for sCRS, with a CRP level of ≥ 20 mg/dL being shown to differentiate patients having sCRS from those with either mild or no CRS (Davila 2014, Lee 2014). Significant elevations in serum ferritin (> 5000 ng/mL) have also been shown to be correlated with sCRS (Grupp 2014). As such, closer observation of subjects is strongly recommended in the setting of a rapidly rising CRP and ferritin and a clinical status concerning for CRS.

These findings, in addition to other published guidelines on the diagnosis and management of CRS (e.g., (Lee 2014)) underlie the toxicity management guidelines provided in this section. In addition, a modification of the Common Terminology Criteria for Adverse Events (CTCAE) CRS grading scale has been established to better reflect CRS associated with administration of 1928z CAR T cells, as detailed in Table 6.

Frequent monitoring for signs and symptoms of CRS, including frequent neurologic examinations, should be performed from the first JCAR015 infusion through the primary response assessment timepoint (28 days after the final JCAR015 infusion). Subjects with fever, especially early onset of fever > 39°C, and a CRP ≥ 10-15 mg/dL should be considered high-risk for developing sCRS and severe neurotoxicity and should be monitored closely for development of symptoms that warrant intervention.

Subjects with Grade 1 or 2 CRS may be managed with supportive care and vigilant monitoring for signs of development of severe CRS. Subjects with early onset of Grade 2 or higher CRS symptoms (i.e., within 96 hours of infusion), including fevers ≥ 39°C, hypotension, neurologic symptoms, and/or rapid elevation in CRP and/or ferritin should be considered high-risk for developing sCRS and should be monitored closely for development of symptoms indicative of sCRS. Prompt medical intervention is essential for subjects with severe CRS (Grade 3 or higher). Importantly, in the setting of early onset of Grade 2 CRS, or in the presence of Grade 3 CRS, both tocilizumab (8 mg/kg) and dexamethasone (10-20 mg IV every 12-24 hours) should be administered.

A detailed CRS management algorithm with guidance for CRS management and use of corticosteroids and/or tocilizumab is provided in Figure 4. This guidance was developed to help avoid life-threatening toxicities while attempting to enable adequate expansion of JCAR015 cells, which appears to be required for an anti-leukemia response. This guidance also emphasizes the importance of early intervention for Grade 2 CRS, or in the setting of a rapid onset or rapid progression of fever and CRS symptoms, to prevent the development of severe (Grade 3 or greater) CRS. Guidelines for the management of CRS are not absolute, and treatment should be individualized based to each subject's clinical needs.

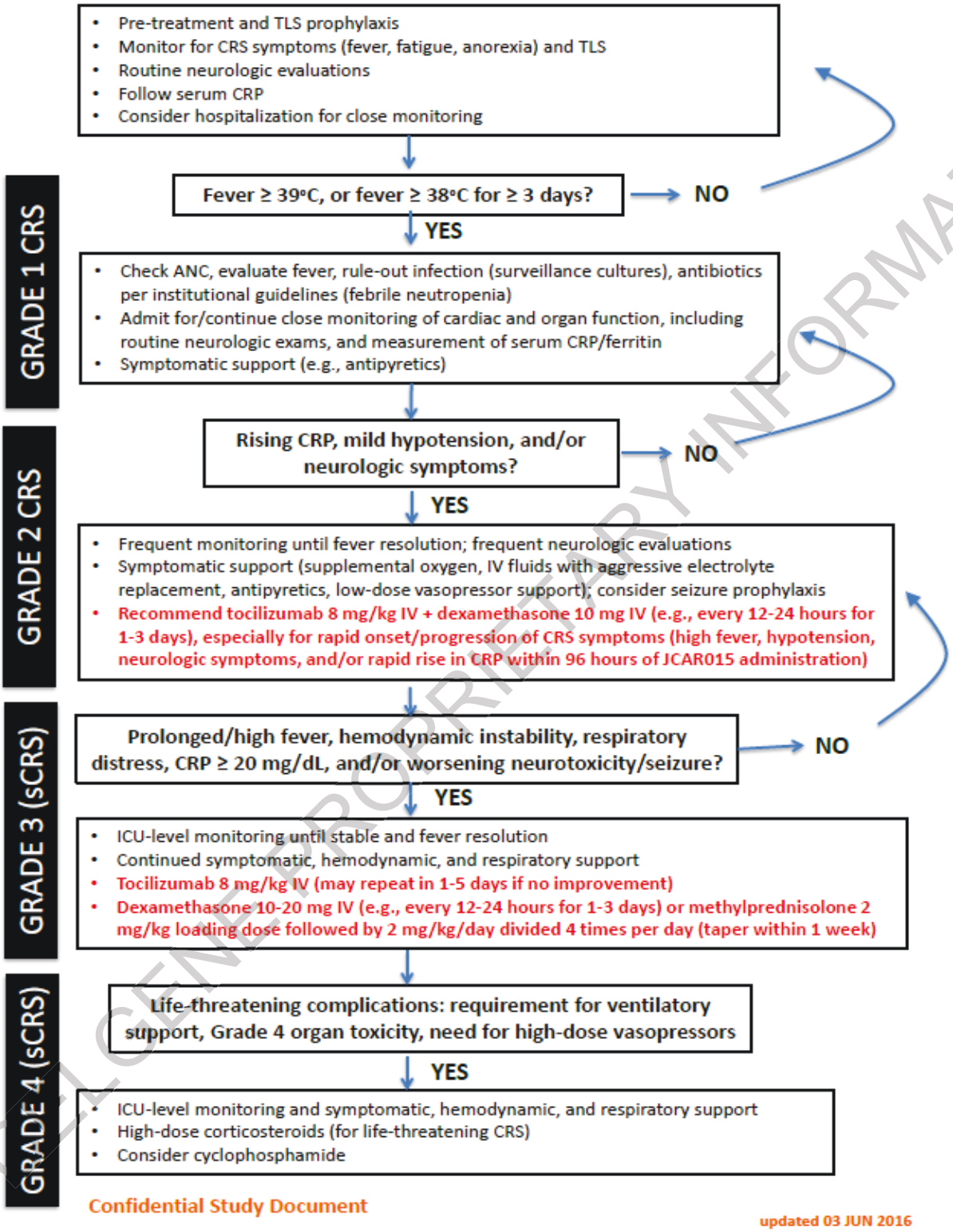
A specific CRF has been developed for recording the signs and symptoms of CRS, severity, management, and response to intervention.

Table 6: Grading Criteria for CRS

Grade	Description of Symptoms
1 Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgias, malaise)
2 Moderate	Require and respond to moderate intervention: • Oxygen requirement < 40%, or • Hypotension responsive to fluids or low dose of a single vasopressor, or • Grade 2 organ toxicity (by CTCAE v4.03)
3 Severe	Require and respond to aggressive intervention: • Oxygen requirement ≥ 40%, or • Hypotension requiring high dose of a single vasopressor (e.g., norepinephrine ≥ 20 µg/min, dopamine ≥ 10 µg/kg/min, phenylephrine ≥ 200 µg/min, or epinephrine ≥ 10 µg/min), or • Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 µg/min norepinephrine), or • Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03)
4 Life-threatening	Life-threatening: • Requirement for ventilator support, or • Grade 4 organ toxicity (excluding transaminitis) (by CTCAE v4.03)
5 Fatal	Death

Adapted from (Lee 2014, Lee 2015a)

Figure 4: CRS Management Algorithm (adapted/modified from (Lee 2014))



7.2 Fever

Subjects who develop a fever (temperature ≥ 38.5 ºC) should be evaluated for infection and treated with antibiotics, fluids, and other supportive care as per institutional or standard clinical practice, and as determined by the Investigator or treating physician. Neutropenic fever should be evaluated promptly (e.g., blood cultures obtained, imaging as clinically required for identification of potential source of infection), and managed medically per institutional or standard clinical practice. Management of a subject with neutropenic fever as an inpatient or outpatient is at the discretion of the Investigator or treating physician. In the event that a subject develops symptoms of systemic bacteremia or sepsis following JCAR015 infusion, blood cultures should be obtained and appropriate medical management initiated.

As noted above, subjects who develop early onset of high fever (temperature ≥ 39ºC within 96 hours of JCAR015 infusion) should be closely monitored for symptoms of CRS and neurologic toxicity. Prompt medical intervention with tocilizumab and dexamethasone should be implemented in the setting of Grade 2 CRS symptoms.

The possibility of CRS should also be considered for all subjects with fever within the first 28 days following each JCAR015 infusion (see Section 7.1). Subjects for whom CRS is suspected and who are not already hospitalized should be considered for hospitalization to facilitate close monitoring of vital signs and neurologic status, as well as symptom management.

7.3 Neurological Toxicities

CAR T-cell therapy, both in the presence and absence of sCRS, has been shown to be associated with neurologic toxicities that are hypothesized to be related to elevated cytokine levels, as opposed to a direct effect of CAR T cells on the CNS. Elevated levels of IL-6 have been implicated, as detailed by Lee et al (Lee 2014). Of note, neurologic symptoms have been observed in subjects with sCRS in which IL-6 is not the primary elevated cytokine.

In some instances, neurologic symptoms may be the earliest symptoms of sCRS; in other cases, these manifestations occur independently of CRS or following CRS. In addition, neurologic symptoms may persist beyond the resolution of CRS symptoms. As such, baseline neurologic examination is essential prior to treatment with JCAR015, and routine neurologic examination should be included for patients at high risk for development of CRS (i.e., those with morphologic evidence of disease at the time of JCAR015 infusion, those with onset of fever ≥ 39°C and CRS symptoms within 96 hours of JCAR015 infusion). In the ongoing MSKCC Phase 1 study (MSKCC Protocol 09-114), levetiracetam has been routinely used for seizure prophylaxis. Data from this study are inconclusive with regard to the efficacy of this intervention in preventing seizures, as some subjects have had EEG-confirmed seizures while receiving levetiracetam prophylaxis. Other ongoing studies of CD19-directed CAR T cells have utilized levetiracetam for subjects felt to be at high risk for seizures.

In general, neurologic symptoms have been seen to begin 5 to 7 days after infusion of CAR T cells. In MSKCC Protocol 09-114, neurologic symptoms began 2 to 32 days after infusion of 1928z CAR T cells. Some of the subjects treated in MSKCC Protocol 09-114 required admission to the ICU for monitoring. Fifteen subjects in the MSKCC 09-114 study experienced Grade 3 or Grade 4 neurotoxicity, including 11 of 31 (35%) subjects with morphologic B-cell ALL at the time of

CAR T cell infusion and four of 20 (20%) subjects with MRD (<5% blasts). There has been no consistent pattern of anatomic changes visible by computed tomography (CT) or magnetic resonance imaging (MRI) in subjects with neurotoxicity in MSKCC Protocol 09-114. The duration of neurologic changes on the MSKCC Phase 1 study ranged from 1 to 38 days, with recovery sometimes occurring after other symptoms of CRS have resolved. While all of the observed neurotoxicity in the MSKCC 09-114 study has been reversible, the time to resolution of neurologic changes does not appear to be hastened by treatment with either tocilizumab or steroids.

Subjects treated with JCAR015 may also develop reversible neurological complications including confusion, delirium, word-finding difficulty, expressive aphasia, obtundation, myoclonus, seizure-like activity, and seizures (confirmed by electroencephalogram [EEG]) (Davila 2014). As described in Section 1.5, three subjects treated with JCAR015 on Protocol 015001 developed severe neurologic toxicities, including Grade 5 cerebral edema, following administration of JCAR015 that was preceded by lymphodepleting chemotherapy with cyclophosphamide in combination with fludarabine.

Subjects receiving JCAR015 should be monitored closely for signs and symptoms of neurological toxicities. Seizures or convulsions should be managed with anti-epileptic drugs as clinically indicated. Management of neurologic toxicity should occur per institutional or standard clinical practice, and as determined by the Investigator or treating physician and/or consulting neurologist. Patients with decreases in level of consciousness may require intervention should they be unable to guard their airway against aspiration. Prophylactic use of antiepileptic drugs (e.g., levetiracetam) should be considered for subjects at the first appearance of symptoms consistent with neurologic toxicity (e.g., confusion, word-finding difficulties, disorientation). In addition, prophylactic administration of levetiracetam prior to JCAR015 infusion should be considered for subjects with a history of seizure disorder or other CNS disorder, as well as those with a history of CNS irradiation or other intensive CNS-directed therapy.

For subjects who have other neurologic manifestations in the absence of symptoms of sCRS, symptomatic care should be administered. For subjects with worsening neurologic changes, corticosteroids may be considered (e.g., dexamethasone 10 mg IV). Tocilizumab and corticosteroids should be considered for subjects with life-threatening neurologic changes. For subjects who have neurologic toxicity in association with CRS, the CRS should be managed utilizing the guidelines provided above. Of note, subjects with early/rapid onset of both CRS symptoms and neurologic symptoms should be treated with both tocilizumab and dexamethasone.

Frequent monitoring for CNS neurotoxicity will be performed throughout the protocol. Subjects will have a thorough neurological examination at screening for both Part A and Part B, and at predefined timepoints after each JCAR015 infusion. Clinical monitoring for neurologic toxicity should not be restricted to predefined data collection timepoints, but should be performed at a frequency based on the subject's risk for toxicity and clinical status. The use of continuous EEG monitoring should be considered based on availability of this capability at the investigational site and on the subject's risk of toxicity and clinical status.

In addition to the baseline neurologic examination and routine follow-up neurologic examinations, neurocognitive assessments will be performed at baseline and at predefined timepoints after each JCAR015 infusion. Neurocognitive assessments will be standardized by employing the Mini

Mental State Examination (MMSE) (Appendix H). The MMSE is a 5- to 10-minute, 11-question measure that examines six areas of cognitive function: orientation, attention, immediate recall, short-term recall, language, and the ability to follow simple verbal and written commands. The MMSE may be administered by an appropriately trained provider (i.e., physician, nurse); a neurologist is not required. Every attempt should be made to dedicate a single research staff member to conduct the assessment to minimize inter-rater variability.

In order to more sensitively detect and more fully define the frequency and reversibility of neurologic toxicity, formal neuropsychological testing, performed by certified and appropriately trained personnel according to the Neuropsychological Test Administration and Training Manual, will be conducted prior to cytoreductive therapy in Part A, and at 2 months and 6 months following the final JCAR015 infusion.

If new neurological symptoms are present, a CSF evaluation (cytology, culture) from a lumbar puncture or Ommaya reservoir tap and/or neuroimaging should be considered in order to rule out abnormalities that may be associated with the subject's underlying disease, prior therapy, or comorbidities.

7.4 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. While MAS has been reported for the T cell-engaging bispecific antibody blinatumomab and the CD19-directed CAR T cell CART19, it has not been observed in the Phase 1 study of 1928z CAR T cells (Grupp 2013, Teachey 2013, Davila 2014). Cytokine-directed therapy (e.g., tocilizumab) was shown to ameliorate the symptoms associated with MAS in these cases (Grupp 2013, Teachey 2013, Davila 2014).

The clinical syndrome of MAS is typically characterized by high-grade non-remitting fever, cytopenias, and hepatosplenomegaly. While there are no definitive diagnostic criteria for MAS, it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (HLH) (Schulert 2014b). The development of MAS is characterized by elevated inflammatory cytokine levels, with the elaboration of numerous pro-inflammatory cytokines (Schulert 2014a). MAS is commonly associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and a decrease of circulating NK cells. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with disseminated intravascular coagulation (DIC). Clinical pathologic features of MAS include the presence of hemophagocytic CD163+ macrophages in bone marrow and lymph node aspirates (Schulert 2014a). Subjects treated with JCAR015 should be monitored for MAS, and use of cytokine-directed therapy should be considered as clinically indicated.

CRS has been associated with biochemical and physiologic abnormalities consistent with MAS, including significant elevations in serum CRP and ferritin. However, the main clinical manifestations of MAS differ from CRS in that they include cytopenias, liver dysfunction, and coagulopathy resembling DIC (Schulert 2014b). MAS should be considered in the evaluation of subjects with symptoms related to CRS. Diagnosis of MAS should be based on published criteria and managed according to published guidelines and as per standard clinical practice (Henter 2007).

7.5 T-Cell Infusion Reactions

Administration of autologous T cell products such as JCAR015 may cause infusion reactions, including fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea. A review by Cruz et al. of AE data from 180 patients who received autologous T cell products on 18 studies over a 10-year period identified no Grade 3 or 4 infusion reactions within 24 hours of T cell administration that were considered related to the T cell product administered (Cruz 2010). Twenty-four related (possibly or definitely) Grade 1 and 2 events occurred in 21 infusions either during the infusion or within the first 6 hours post-infusion. An additional 22 related events occurred between 6 and 24 hours post-infusion. No SAEs were reported that were considered related to the T cell product administered. Among the 46 related events that occurred in total, the most commonly reported events were nausea/vomiting and hypotension. To date, no T cell infusion reactions have been observed in any subject treated with 1928z CAR T cells.

As noted in Section 6.3.10, to minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen or diphenhydramine or both (at the discretion of the Investigator) 30 to 60 minutes prior to each JCAR015 infusion. Mild infusion reactions (CTCAE Grade 1) should be managed expectantly with antipyretics, antihistamines, and antiemetics, as clinically indicated. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR015 cells. Rigors may be treated with meperidine 12.5 to 50 mg intravenously. Nausea and vomiting may be treated using institutional standard of care guidelines.

For CTCAE v4.03 Grade 2 or greater infusion reactions, the following guidelines should be followed for the management of infusion reactions:

- Grade 1 reaction: administer symptomatic treatment; continue JCAR015 infusion at the same dose and rate of infusion
- Grade 2 reaction: administer symptomatic treatment; continue JCAR015 infusion with a 50% reduction in the infusion rate
- Grade 3 reaction: stop JCAR015 infusion, administer symptomatic treatment, and resume at 50% reduction in the initial infusion rate only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCAR015 infusion.
- Grade 4 reaction: discontinue JCAR015 infusion and administer symptomatic treatment as necessary; no further JCAR015 will be administered.

Of note, JCAR015 stability at room temperature is 3 hours after thawing (see Section 6.3.11). Time post-thawing should be carefully monitored in the event that the JCAR015 infusion has to be temporarily halted to address an infusion reaction.

7.6 Tumor Lysis Syndrome

Both the cytoreductive chemotherapy employed in this protocol and JCAR015 may cause TLS, a potentially life-threatening condition associated with the treatment of hematologic malignancies. Toxicities, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, develop as antileukemia therapy causes lysis of tumor cells, resulting in release of intracellular contents into the bloodstream. If not recognized promptly and managed appropriately, renal insufficiency, cardiac arrhythmias, seizures, and death can occur (Howard 2011). The incidence

of TLS is increased in hematologic cancers that have a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy.

Successful management of TLS includes identification of subjects at high risk for developing TLS (those with high disease burden, and those with high cell turnover as indicated by an elevated uric acid and/or lactate dehydrogenase [LDH]), initiation of prevention strategies, and the early identification of acute kidney injury (AKI) prior to the traditional increase in serum creatinine. All play a role in limiting the extent of TLS-related AKI. As such, subjects will be closely monitored over the course of the study for evidence of TLS from the start of cytoreductive chemotherapy and followed thereafter based on published guidance (Cairo 2004), including blood tests for serum potassium and uric acid levels. Appropriate clinical therapy should be administered promptly should any significant tumor lysis occur.

TLS prophylaxis is strongly recommended as described in Section 6.4. Hydration and effective urine flow rates remain the cornerstone of TLS prevention, and treatment should be employed as per institutional standards, in addition to medications to prevent or treat hyperuricemia (e.g., allopurinol, rasburicase, febuxostat).

In the event of TLS, immediate treatment must be administered according to institutional standards, including hydration, administration of xanthine oxidase inhibitors or rasburicase, supportive care for electrolyte disturbances, and hemodialysis or hemofiltration if required. For subjects with renal insufficiency, a nephrologist should be consulted.

7.7 B-cell Aplasia

B-cell aplasia is a potential and expected off-tumor, on-target toxicity, arising from targeted elimination of non-malignant CD19+ B cells. While prolonged B-cell aplasia has been observed in preclinical mouse studies of 1928z CAR T cells and with other CD19-directed CAR T cell programs (Davila 2013, Grupp 2013), it has not been observed in the MSKCC Phase 1 study. The main risk of B-cell aplasia is hypogammaglobulinemia which may increase the risk of infection. This toxicity may be managed by monitoring of serum immunoglobulin levels and infusion of intravenous immunoglobulin (IVIG) as clinically indicated.

CD19-targeted CAR T cells have been demonstrated in other studies to also eliminate normal B cells resulting in hypogammaglobulinemia. Therefore, serum immunoglobulin levels will be obtained from all subjects prior to and at various timepoints following JCAR015 therapy. Hypogammaglobulinemic subjects (serum IgG <500 mg/dL) should be considered for IVIG replacement therapy at a dose of 500 mg/kg with appropriate premedications, per institutional guidelines.

7.8 GVHD

The likelihood of graft versus host disease (GVHD) occurring is low, but it is a theoretical risk with CAR T cell therapy. Studies of activated donor lymphocyte infusions (ex vivo activated lymphocytes collected from the donor for patients who have undergone allogeneic HSCT, grown in a similar manner as JCAR015 but without CAR transduction) showed a low rate of GVHD (Porter 2006). To date, there have been no reported cases of GVHD with administration of 1928z CAR T cells or with other CD19-directed CAR T cell programs.

Patients who have undergone allogeneic transplant and who have active, acute or chronic GVHD at screening are excluded from enrolling in this protocol. However, due to the possibility of some degree of residual donor engraftment, which will include T cells of donor origin, subjects that received a previous HSCT will be assessed for donor chimerism at screening and will be monitored closely throughout the study for signs of GVHD.

7.9 Replication-Competent Retrovirus

Replication-competent retrovirus (RCR) may be generated during the JCAR015 manufacturing phase or subsequently after introduction of vector-transduced cells into study subjects. However, an RCR resulting from the production phase is highly unlikely since measures are taken to minimize vector recombination and generation of RCR. Furthermore, the vector used to transduce the cell product undergoes sensitive assays for the detection of RCR prior to release to subjects. Nonetheless, RCR generation following infusion of the vector product into a subject remains a theoretical possibility. The consequences of such recombination events in subjects without a known retroviral infection are unknown, and therefore subjects with co-existent HIV infection and/or active hepatitis C infections are excluded from participation in this study in order to minimize this possibility. The development of RCR could pose a risk to both the subject and his or her close contact(s) therefore, monitoring for RCR will be conducted during the course of this study.

Samples will undergo GaLV-RCR testing as per Appendix B. Peripheral blood samples will be sent for RCR testing during screening for Part B; at 3, 6, and 12 months following completion of therapy; and at relapse (if applicable). Additional blood samples will be archived annually for up to 15 years following therapy and tested only if RCR is detected within the first 12 months from treatment as per FDA guidelines (Food and Drug Administration 2000).

7.10 Uncontrolled T-Cell Proliferation

CAR T cells, including JCAR015, could theoretically proliferate without control of normal homeostatic mechanisms. To date, preclinical and clinical data from studies using 1928z CAR T cells have shown proliferation only in response to stimulation with CD19 antigen or in response to normal T cell physiologic signaling (Brentjens 2011, Davila 2014, Park 2014). It is anticipated that JCAR015 cells will proliferate in response to CD19-positive leukemia cells and to normal CD19-positive B cells. The former is necessary for the intended therapeutic effect.

If uncontrolled JCAR015 T cell proliferation occurs (e.g., expansion of JCAR015 cells in the absence of CD19 antigen), subjects may be treated with high-dose corticosteroids (e.g., methylprednisolone 2 mg/kg/day IV/IM, tapered over 2-3 weeks) or with lymphodepleting doses of cyclophosphamide (1.0 to 3.0 g/m^2 IV). If investigators suspect uncontrolled JCAR015 proliferation, the Sponsor should be contacted immediately. It should be noted that this theoretical toxicity is separate and distinct from the CRS that develops during the expected, antigen-driven T-cell proliferation that occurs upon exposure to CD19-positive leukemic cells. CRS should be managed according to the guidelines detailed in Section 7.1.

7.11 Clonality and Insertional Oncogenesis

Risks of gene therapy also include insertional mutagenesis. While insertional mutagenesis is theoretically possible using retroviral vectors, this has only been observed in the setting of infants treated for X-SCID using retroviral vector-mediated gene transfer into CD34+ bone marrow stem cells. In the case of retroviral vector-mediated gene transfer into mature T cells, there has been no evidence of long- term toxicities associated with these procedures since the first NCI-sponsored gene transfer study in 1989. Despite the fact that currently available clinical data suggest that the introduction of retroviral vectors transduced into mature T cells is a safe procedure, continued follow-up of all gene therapy subjects will be performed as required. The proposed protocol follows all current FDA guidelines regarding testing and follow-up of subjects receiving gene-transduced cells. Similarly, the viral vectors used have been engineered to minimize the risk of emergence of replication competent retrovirus, but subjects will be monitored according to Recombinant DNA Advisory Committee guidelines for several years following receipt of this therapy; in the case of the development of second malignancy, all efforts will be made to determine whether replication competent retrovirus has emerged.

7.12 Chemotherapy-Associated Risks

7.12.1 Risks Associated with Cytoreductive Chemotherapy

Based on the clinical judgment of study investigators, subjects may receive cytoreductive chemotherapy after enrollment and leukapheresis in order to maintain disease control while JCAR015 cell product is being generated.

Risks associated with the cytoreductive chemotherapy agents and regimens listed in this protocol have been previously described, and include myelosuppression, anemia, thrombocytopenia, and immunosuppression. In addition, the reduction of humoral immunity by the targeting and lysis of normal B cells may exacerbate the risk of infection. Subjects should be considered for growth factor support (e.g., filgrastim or pegfilgrastim) as clinically indicated. Thrombocytopenia should be managed with platelet transfusions at the discretion of the treating physician. Subjects will receive prophylactic antibiotics and antifungal agents as clinically indicated. Neutropenic fevers should be managed with broad-spectrum intravenous antibiotics as per standard clinical practice guidelines. Hospitalization for febrile neutropenia is at the discretion of the treating physician. Subjects may be considered for IVIG therapy in the setting of hypogammaglobulinemia. The chemotherapy drugs employed in some of these regimens may less commonly cause cardiotoxicity, hemorrhagic cystitis, SIADH, and secondary malignancies. Subjects will be monitored for these toxicities and managed appropriately if they occur, as per standard clinical practice and/or institutional guidelines.

7.12.2 Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive cyclophosphamide prior to JCAR015 infusion to facilitate lymphodepletion and CAR T cell engraftment. Toxicity from cyclophosphamide includes bone marrow suppression, which usually occurs 10 to 12 days after administration; nausea; vomiting; anorexia; abdominal discomfort; diarrhea; stomatitis; hemorrhagic colitis; jaundice; reversible alopecia; hemorrhagic cystitis, which can frequently be prevented with increased hydration; hematuria; ureteritis; tubular

necrosis; fibrosis of the bladder; cardiac toxicity, which may potentiate existing doxorubicin-induced cardiotoxicity; rare anaphylactic reaction; skin rash; hyperpigmentation of the skin and nails; interstitial pulmonary fibrosis; and cross-sensitivity with other alkylating agents.

Treatment with cyclophosphamide may cause significant suppression of the immune system. Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other antineoplastic drugs. These may occur several years after treatment has been discontinued.

Administration of cyclophosphamide, as well as monitoring and management of cyclophosphamide-associated toxicities, should be performed per standard clinical practice and/or institutional guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Schedule of Events

Detailed tables of study evaluations to be conducted at each study visit are provided in Appendix A (Part A) and Appendix B (Part B).

8.2 Study Visits

8.2.1 Part A

8.2.1.1 Screening

The following assessments will be conducted up to 4 weeks prior to administration of cytoreductive chemotherapy (if applicable):

- Obtain informed consent
- Review of inclusion and exclusion criteria for Part A
- Complete medical history including prior and current medical conditions
- Confirmation of diagnosis including leukemia-specific history (including results from the most recent bone marrow examination, including cytogenetics, fluorescence in situ hybridization [FISH], and tumor immunophenotyping by flow cytometry)
- History of prior anticancer treatment regimens including stem cell transplant history (if applicable)
- Concomitant anticancer medications and other concomitant medications associated with an SAE
- Complete physical exam, including neurologic examination, height, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) and GVHD assessment (if applicable). Physical examination should focus upon sites of extramedullary disease involvement and should include assessment for CNS symptoms.
- ECOG performance status
- MUGA scan or cardiac echocardiogram (ECHO) (performed within 1 month of enrollment) for LVEF
- 12-Lead electrocardiogram (ECG)
- Chest x-ray
- Neuropsychological assessment (performed prior to cytoreductive chemotherapy)
- Head CT or MRI (if clinically indicated)
- Collection of peripheral blood samples for clinical laboratory evaluations and serum pregnancy test (see Appendix A)
- HLA typing (if results not available from a prior test)
- Urinalysis

- Collection of bone marrow aspirate and biopsy samples for morphologic evaluation and biomarker evaluations (see Appendix A and Table C-2 in Appendix C)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow)
- Lumbar puncture or Ommaya reservoir tap for CSF assessment (see Appendix A and Table C-3 in Appendix C)
- SAEs

8.2.1.2 Leukapheresis

On the day of leukapheresis, the following assessments should be conducted:

- Concomitant medications associated with an SAE
- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Weight
- SAEs

8.2.1.3 Cytoreductive Chemotherapy

Prior to JCAR015 infusion but after leukapheresis, cytoreductive chemotherapy may be administered (see Section 6.2). The choice of regimens will be selected by the Investigator from the regimens specified in Section 6.2 and will be dependent on the subject's disease burden.

When given, cytoreductive chemotherapy should be started after leukapheresis. Timing of chemotherapy administration and hematopoietic recovery should be taken into consideration such that JCAR015 may be administered within 14 to 28 days after the initiation of the chemotherapy if possible. Subjects with Ph+ ALL who receive a TKI should be treated at least through notification of JCAR015 product availability.

Pre-chemotherapy physical examination and laboratory evaluation should be performed as per institutional and standard clinical practice.

8.2.2 Part B

8.2.2.1 Screening (Day -18 to Day -2)

Subjects experiencing toxicities or illnesses during Part A may have their JCAR015 infusion schedule delayed for up to 12 weeks after the initiation of cytoreductive chemotherapy until these toxicities have resolved. The JCAR015 infusion schedule may be delayed for up to 8 weeks after the initiation of cytoreductive chemotherapy to accommodate subjects who require additional time to make travel or logistical arrangements. The following assessments will be conducted within 10 days prior to administration of lymphodepleting chemotherapy:

- Review of inclusion and exclusion criteria for Part B
- Concomitant medications associated with an SAE
- Complete physical exam, including neurologic examination, weight, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via

pulse oximetry) and GVHD assessment (if applicable). Physical examination should focus upon sites of extramedullary disease involvement and should include assessment for CNS symptoms.

- ECOG performance status
- MUGA scan or ECHO (if clinically indicated)
- 12-Lead ECG (if clinically indicated)
- Head CT or MRI (if clinically indicated)
- Chest x-ray (if clinically indicated)
- MMSE
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations and baseline RCR assessment (see Appendix B and Table C-1 in Appendix C)
- Skin biopsy to provide matched normal genomic DNA for sequencing studies (see Appendix B and Table C-2 in Appendix C)
- Collection of bone marrow aspirate and bone marrow biopsy samples for:
  - Morphologic assessment of response to cytoreductive therapy (if applicable)
  - Biomarker evaluations (see Appendix B and Table C-2 in Appendix C)

  Note: If lymphodepleting chemotherapy is initiated more than 10 days after the bone marrow examination conducted at Part B screening, the bone marrow examination must be repeated prior to administration of lymphodepleting chemotherapy.
- Serum or urine pregnancy test
- Lumbar puncture or Ommaya reservoir tap for CSF assessment (cytology) (if clinically indicated)
- FACT-Leu questionnaire (see Appendix F)
- SAEs

8.2.2.2 Lymphodepleting Chemotherapy (Dose #1 Day -5 to Day -2)

Lymphodepleting chemotherapy with a single dose of cyclophosphamide (1.0 to 3.0 g/m^2 IV) will be administered 2 to 5 days prior to the first JCAR015 infusion (see Section 6.3.9 for details).

On the day of, but prior to, the cyclophosphamide infusion, subjects should undergo blood tests necessary for the safe administration of chemotherapy as per institutional or standard clinical practice. In addition, the following assessments will be conducted and collected:

- Concomitant medications
- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- AEs

8.2.2.3 JCAR015 Dose #1 (Dose #1 Day 1)

JCAR015 will be administered 2 to 5 days after cyclophosphamide administration as described in Section 6.3.12. Subjects experiencing toxicities from their preceding lymphodepleting chemotherapy may have their JCAR015 infusion schedule delayed up to 7 days after completion

of lymphodepleting chemotherapy until these toxicities have resolved. If a delay of greater than 7 days is required, lymphodepleting chemotherapy and assessments listed in Section 8.2.2.2 should be repeated for subjects with a WBC ≥ 1000/μL.

On the day of, but prior to, the JCAR015 infusion, the following assessments will be conducted:

- Concomitant medications
- Physical examination, including neurologic examination, assessment of CNS symptoms, and weight
- ECOG performance status
- MMSE

Collection of peripheral blood samples for clinical laboratory and biomarker evaluations (see Appendix B and Table C-1 in Appendix C). In addition, the following assessments will also be conducted at this visit:

- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) will be measured within 15 minutes prior to, during, and within 15 minutes after the infusion, and then every 15 minutes thereafter for the first hour, and hourly for the next 3 hours. If the subject's vital signs are not stable 4 hours following JCAR015 infusion, vital signs should be monitored as clinically indicated until stable.
- AEs

8.2.2.4 Post-Dose #1 Monitoring (Day 2, Day 4±1, Day 7±1, Day 11±1, Day 14±1, Day 21±2, and Day 28±2)

At Post-Dose #1 Days 2, 4, 7, 11, and 14 (and Day 21 and Day 28 for subjects who have not received JCAR015 Dose #2 by these study days), subjects will undergo the following assessments:

- Concomitant medications
- Physical examination, including neurologic examination, assessment of CNS symptoms, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Assessment of extramedullary disease (Day 28 only)
- ECOG performance status (Days 7, 14, 21, and 28 only)
- MMSE
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations (see Appendix B and Table C-1 in Appendix C)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow) (Days 14 and 28 only)
- FACT-Leu questionnaire (Day 28 only)
- AEs

On Post-Dose #1 Day 14 only, a bone marrow aspirate and biopsy will be performed on all subjects for MRD assessment and biomarker evaluations (see Table C-2 in Appendix C).

On Post-Dose #1 Day 28, subjects who have not received Dose #2 of JCAR015 by Day 28 post-Dose #1 will have a bone marrow aspirate and biopsy performed for disease response assessment and biomarker evaluations. These subjects will also have a CSF assessment for response evaluation.

8.2.2.5 Pre-Dose #2: Lymphodepleting Chemotherapy for Subjects with WBC ≥ 1000/µL (Dose #2 Day -5 to Day -2)

Dose #2 of JCAR015 should be administered 14 to 28 days after Dose #1. Subjects experiencing toxicities or other illnesses after Dose #1 of JCAR015 may have Dose #2 of JCAR015 delayed until these toxicities have resolved. Subjects whose toxicities do not resolve by 8 weeks after Dose #1 will be withdrawn from further study treatment (see Section 4.4.1), but will continue to have all assessments scheduled for Post-Infusion Monitoring. Subjects who have not received Dose #2 by Post-Dose #1 Day 21 and/or Day 28 should complete all assessments listed for the Post-Dose #1 Day 21 and Day 28 visits, respectively, as indicated in Appendix B.

Subjects with a WBC ≥ 1000/µL may receive lymphodepleting chemotherapy with a single dose of cyclophosphamide (1.0 to 3.0 g/m^2 IV) 2 to 5 days prior to the second JCAR015 infusion at the discretion of the Investigator (see Section 6.3.9 for details). On the day of, but prior to, the cyclophosphamide infusion, subjects should undergo blood tests necessary for the safe administration of chemotherapy as per institutional or standard clinical practice. In addition, the following assessments will be conducted and collected:

- Concomitant medications
- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- AEs

8.2.2.6 JCAR015 Dose #2 (Dose #2 Day 1)

Dose #2 of JCAR015 will be administered 2 to 5 days after cyclophosphamide administration (for subjects who receive a second course of lymphodepleting chemotherapy based on WBC ≥ 1000/µL) or 14 to 28 days after Dose #1 of JCAR015 (for subjects who do not receive a second course of lymphodepleting chemotherapy) as described in Section 6.3.12. Subjects experiencing toxicities from their second dose of lymphodepleting chemotherapy may have their JCAR015 infusion schedule delayed up to 7 days after completion of lymphodepleting chemotherapy until these toxicities have resolved. If a delay of greater than 7 days is required, lymphodepleting chemotherapy and the assessments listed in Section 8.2.2.5 should be repeated for subjects with a WBC ≥ 1000/µL.

On the day of, but prior to, Dose #2 of JCAR015, the following assessments will be conducted:

- Concomitant medications
- Physical examination, including neurologic examination and assessment of CNS symptoms
- Weight
- ECOG performance status

- MMSE
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations (see Appendix B and Table C-1 in Appendix C)

In addition, the following assessments will also be conducted at this visit:

- Vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry) will be measured within approximately15 minutes prior to, during, and within 15 minutes after the infusion, and then every 15 minutes thereafter for the first hour, and hourly for the next 3 hours. If the subject's vital signs are not stable 4 hours following JCAR015 infusion, vital signs should be monitored as clinically indicated until stable.
- AEs

8.2.2.7 Post-Dose #2 Monitoring (Day 2, Day 4±1, Day 7±1, Day 11±1, and Day 14±1, Day 21±2, Day 28±2)

At Post-Dose #2 Days 2, 4, 7, 11, 14, 21, and 28, subjects will undergo the following assessments:

- Concomitant medications
- Physical examination, including neurologic examination, assessment of CNS symptoms, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Assessment of extramedullary disease (Day 28 only)
- MMSE
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations (see Appendix B)
- AEs
- ECOG performance status (Days 7, 14, 21, and 28 only)
- Lumbar puncture or Ommaya reservoir tap for CSF assessment (Day 28 only; see Appendix B and Table C-3 in Appendix C)
- FACT-Leu questionnaire (Day 28 only)
- Collection of bone marrow aspirate and biopsy samples for disease response assessment and biomarker evaluations (see Appendix B and Table C-2 in Appendix C) (Day 28 only)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow) (Day 28 only)

8.2.3 Post-Infusion Monitoring (Month 2 through Month 9)

The following assessments will be conducted at 2, 3, 4, 5, 6, and 9 months (±14 days) after the final dose of JCAR015 (i.e., Post-Dose #2 for subjects that receive both infusions or Post-Dose #1 for subjects that receive only one infusion):

- Concomitant medications

- Physical examination, including neurologic examination, assessment of CNS symptoms, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Assessment of extramedullary disease
- ECOG performance status
- MMSE (at the 3-, 6-, and 9-month visits only)
- Neuropsychological assessment (at the 2- and 6-month follow-up visits only)
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations (see Appendix B and Table C-1 in Appendix C)
- Collection of peripheral blood for RCR testing (at the 3- and 6-month follow-up visits only)
- Collection of bone marrow aspirate and biopsy samples for disease response assessment and biomarker evaluations (at the 3- and 6-month follow-up visits as indicated in Appendix B and Table C-2 in Appendix C)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow) (at the 3- and 6-month follow-up visits only)
- CSF assessment as clinically indicated at the 3- and 6-month follow-up visits only
- Head CT or MRI (as clinically indicated)
- AEs
- FACT-Leu questionnaire (at the 3-, 6-, 9-month follow-up visits only)

8.2.4 Unscheduled Visits

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit days, the subject may be requested to come in for an unscheduled visit. At each unscheduled visit, the following assessments should be conducted:

- Concomitant medications
- Physical examination, including neurologic examination (if clinically indicated), vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- Collection of peripheral blood samples for clinical laboratory evaluations (if clinically indicated; see Appendix B)
- AEs
- Bone marrow aspirate and biopsy (if clinically indicated)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow)
- CSF assessment (if clinically indicated)

Results from any unscheduled laboratory evaluations, bone marrow examination (aspirate and/or biopsy), or lumbar puncture/Ommaya reservoir tap should be captured in the appropriate CRF(s).

8.2.5 End-of-Study Visit (Month 12±14 days)

An EOS visit will be scheduled at 12 months (±14 days) after the final JCAR015 infusion (i.e., Dose #2 for subjects that complete treatment and Dose #1 for subjects that receive only one dose of JCAR015). The following assessments will be conducted at this visit:

- Concomitant medications
- Physical examination, including neurologic examination, assessment of CNS symptoms, assessment of extramedullary disease, and vital signs (blood pressure, body temperature, respirations, heart rate, and oxygen saturation via pulse oximetry)
- ECOG performance status
- MMSE
- Neuropsychological assessment (only for subjects that withdraw prior to the Month 6 assessment)
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations and RCR testing (see Appendix B and Table C-1 in Appendix C)
- Collection of bone marrow aspirate and biopsy samples for disease response assessment and biomarker evaluations (see Appendix B and Table C-2 in Appendix C)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow)
- CSF assessment (as clinically indicated)
- Head CT or MRI (as clinically indicated)
- AEs
- FACT-Leu questionnaire

8.2.6 Relapse Evaluation

For all subjects in Part B who achieve remission following JCAR015 infusion and subsequently relapse prior to the EOS visit, a full disease evaluation will be completed. The following assessments will be performed as soon as possible after suspicion of, or diagnosis of, relapse:

- Concomitant medications
- Physical examination (with a focus on extramedullary disease assessment), including neurologic examination, assessment of CNS symptoms, and vital signs
- ECOG performance status
- FACT-Leu
- Collection of peripheral blood samples for clinical laboratory and biomarker evaluations and RCR testing (see Appendix B and Table C-1 in Appendix C)
- Collection of bone marrow aspirate and biopsy samples for biomarker evaluations (see Appendix B and Table C-2 in Appendix C)
- Karyotype and FISH analysis (peripheral blood or bone marrow)
- BCR-ABL qPCR for Ph+ subjects (peripheral blood or bone marrow)
- Lumbar puncture or Ommaya reservoir tap for CSF assessment (see Appendix B and Table C-3 in Appendix C)

- MMSE
- Neuropsychological assessment (only for subjects who relapse prior to the Month 6 assessment)
- Head CT or MRI (as clinically indicated)
- AEs

Subjects who relapse before the EOS visit may be removed from the study but will continue to be followed for survival and RCR testing on a separate LTFU protocol.

8.2.7 Early Withdrawal

If a subject withdraws prematurely from the study (Section 4.4.2), a visit will be scheduled as soon as possible and all of the assessments listed for the EOS visit will be performed. A reason for early withdrawal will be captured in the CRF.

8.2.8 Long-Term Follow-Up

As JCAR015 is administered as a single course of treatment, subjects are followed on study for 1 year after the final JCAR015 infusion for safety and efficacy evaluations. Because this protocol involves gene transfer, long-term follow-up for retroviral vector safety and persistence, and long-term survival will continue under a separate LTFU protocol for up to 15 years after the final JCAR015 infusion per health authority guidelines.

Under the LTFU protocol, and consistent with CBER/BRMAC recommendations for gene transfer research protocols, annual evaluations will be performed on all subjects who receive a JCAR015 cell product infusion. All subjects who either complete the primary follow-up period specified in this Phase 2 protocol or who prematurely withdraw after at least one JCAR015 infusion will be asked to participate in this LTFU protocol at the EOS visit or at the time of withdrawal, respectively. In addition, subjects who proceed to HSCT prior to completion of the primary follow-up period will be withdrawn from the study and asked to enroll in the LTFU protocol at the time of withdrawal. A separate informed consent form (ICF) will be provided for the LTFU protocol. Subjects who do not consent to participate in the LTFU protocol will be followed for survival through public record and date of death will be entered into the appropriate CRF.

In the LTFU protocol, subjects will undergo a routine (semi-annual or annual) physical examination and medical history, including concomitant medications and AEs, with particular attention paid to features possibly related to retrovirus-associated events such as new malignancies, new incidence or exacerbation of a pre-existing neurologic disorder, new incidence or exacerbation of a prior rheumatologic or autoimmune disorder, or new incidence of other hematologic disorders. Bone marrow examinations may be performed to evaluate or confirm remission status. In addition, laboratory studies will be performed to evaluate routine safety endpoints, JCAR015 vector persistence, and RCR.

8.3 Study Assessments

8.3.1 Efficacy Assessments

Disease assessments by bone marrow examination (aspirate and biopsy for morphologic assessment) will be performed at 28 days after completion of the final infusion of JCAR015 (i.e., Dose #2 for subjects that complete JCAR015 treatment, and Dose #1 for subjects that receive only one dose). If the subject is not in a CR or CRi at this time, a repeat marrow examination should be performed when there is evidence of hematopoietic recovery so that remission can be assessed. Repeat bone marrow examinations will be performed at Months 3, 6, and 12 after the final JCAR015 infusion, or until the subject requires alternative therapy for his or her disease.

Clinical response will be assessed according to NCCN guidelines for ALL (National Comprehensive Cancer Network 2014) and the International Working Group (IWG) guidelines for acute myeloid leukemia (Cheson 2003) based on assessments of the bone marrow and peripheral blood, physical examination, evaluation of central nervous system (CNS) symptoms, and examination of the cerebrospinal fluid (CSF) (see Appendix G for details on response assessment). Minimal residual disease assessment will be performed using IgH gene sequencing methodology to assess depth of remission and to describe the quantity, kinetics, immunophenotype, and distribution of malignant clones before and after JCAR015 infusion.

In order for the best overall disease response to be categorized as CR or CRi, there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical exam and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. Any additional assessments (e.g., bone marrow, CSF assessment by lumbar puncture or Ommaya reservoir tap, CNS imaging, biopsy, etc.) performed for the purpose of disease response evaluation must also support a response of remission.

8.3.2 Physical Examination

A physical examination, including a neurological examination, will be conducted at specified timepoints indicated in the schedule of events tables (Appendix A and Appendix B). At screening and at each visit for response assessment, the exam should also include an assessment of the presence of extramedullary disease (i.e., hepatomegaly, splenomegaly, skin/gum infiltration, testicular masses).

Significant physical exam findings identified during screening for Part A should be recorded in the medical history CRF. The disease response assessment results will be recorded in the appropriate CRF. Significant abnormalities that begin or worsen after initiation of study treatment must be recorded as AEs, as defined in Section 9.1. Height will be recorded at screening; weight will be recorded at timepoints specified in Appendix A and Appendix B.

8.3.3 Concomitant Medications

Prescription medications taken by the subject from the time of the first dose of lymphodepleting chemotherapy in Part B through 90 days after the final JCAR015 infusion will be recorded in the subject's medical record and CRF. After 90 days post-infusion, only the following concomitant medications will be recorded in the subject's medical record and CRF:

- Corticosteroids
- Medications for the treatment of GVHD
- Anticancer therapies
- Medications used to treat related AEs

Medications used to treat SAEs will be recorded from the time of informed consent through 30 days after the final infusion of JCAR015. After 30 days following the final JCAR015 infusion through the EOS visit, medications used to treat SAEs will only be recorded for SAEs considered related to JCAR015.

8.3.4 CNS and CSF Evaluations

CSF will be assessed by lumbar puncture or Ommaya reservoir tap at the timepoints indicated in Appendix A and Appendix B. In addition, CSF assessments will be performed after JCAR015 infusion as clinically indicated (e.g., if new CNS symptoms occur, or if clinical signs or suspicion of CNS leukemia exist). CSF will be analyzed for cell count and differential cytology, and for the presence of JCAR015 product. CSF cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

Assessment of neurologic symptoms suggestive of leukemic involvement of the CNS (e.g., meningismus, cognitive impairment, severe headache) that occur in the absence of other apparent etiologies should be performed and recorded with each physical examination.

A Mini Mental State Examination (MMSE) should be performed and scored at the indicated timepoints using the template provided (see Appendix H for a copy). The MMSE may be administered by an appropriately trained provider (i.e., 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.

A neuropsychological assessment should be performed by certified and appropriately trained personnel. Neuropsychological assessments will administered to English-speaking subjects only. Neuropsychological assessments will be collected at timepoints specified in Appendix A and Appendix B.

CNS imaging (CT and/or MRI) scans collected to evaluate neurotoxicity will be submitted to an imaging vendor selected by Juno and held for central review.

8.3.5 Safety Assessments

Safety will be monitored by physical examination, laboratory evaluation, neurologic examination, as well as by reviewing AEs at every visit. Details for AE collection and reporting are provided in Section 9.

8.3.5.1 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at screening and at other timepoints according to Appendix A and Appendix B. Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs or expected events.

The Investigator will assess the clinical significance of each applicable laboratory value that falls outside of the institutional reference range. This decision should be based upon the nature and degree of the observed laboratory abnormality. Values that are considered by the Investigator to be clinically significant will be reported as an AE. The Investigator may choose to repeat any abnormal test once in order to rule out laboratory or sample collection error.

Any unscheduled laboratory value occurring from the first JCAR015 infusion to 30 days after the final JCAR015 infusion that is determined to be clinically significant and is associated with an AE or SAE should be recorded on the appropriate CRF. In addition, all other laboratory results from the same panel as the laboratory result meeting the criteria above should also be recorded.

Any unscheduled inflammatory marker result (i.e., CRP and/or ferritin) occurring within 30 days after the final dose of JCAR015 should also be recorded even if the result is not abnormal.

Details regarding the panels of analytes to be measured for clinical laboratory evaluations are provided in Appendix D.

8.3.5.2 Vital Signs

Vital signs will be assessed at specified timepoints and will include the following measurements:

- Body temperature
- Blood pressure, heart rate, and respiration rate
- Oxygen saturation by pulse oximetry

Subjects who require hospitalization should have vital signs assessed daily. Minimum and maximum values within a 24-hour period should be recorded on the appropriate CRF.

8.3.5.3 Height and Weight

Height in centimeters and body weight (measured to the nearest 0.1 kilogram) will be measured. The body weight obtained on the day of leukapheresis will be used for JCAR015 manufacturing and dosing purposes.

8.3.5.4 ECOG Performance Status

The ECOG performance status (see Table 7) will be used to evaluate subject eligibility at screening and will be assessed throughout the study at timepoints specified in Appendix A and Appendix B.

Table 7: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Adapted from (Oken 1982)

8.3.5.5 MUGA/Echocardiogram

An assessment of LVEF will be performed by echocardiogram or MUGA at Part A screening in order to assess the cardiac function of the subject and to confirm study eligibility. If clinically indicated, LVEF assessment will be repeated at Part B screening. Subjects must exhibit an LVEF ≥ 40% as confirmed by echocardiogram or MUGA. All abnormalities that are clinically significant will be recorded on the subject's Medical History CRF.

8.3.5.6 Electrocardiogram

A standard 12-lead ECG should be obtained at Part A screening and, if clinically indicated, repeated at Part B screening. ECG tracings should be labeled with the study number, subject number, date, and Investigator's signature, and kept in the source documents at the study site. All abnormalities that are clinically significant will be recorded on the subject's Medical History CRF.

8.3.5.7 Chest X-Ray

A standard posterior-anterior (PA) and lateral chest x-ray should be obtained at Part A screening and as clinically indicated during Part B screening. All clinically significant abnormalities will be recorded on the subject's Medical History CRF.

8.3.6 Pharmacokinetic Assessments

The assessment of JCAR015 cellular pharmacokinetics will quantify the number and proportion of mononuclear cells, isolated from blood, bone marrow aspirate, or CSF, that express the JCAR015 transgene by qPCR. In addition, the number and immunophenotype of JCAR015 cells in blood, bone marrow aspirate, and CSF will be determined by cell surface expression of the transgene product as detected by flow cytometry. The assessment of JCAR015 cellular kinetics will be used to examine possible relationships between the persistence and expansion of JCAR015 and safety and efficacy. Peripheral blood, bone marrow, and CSF will be collected as indicated in Appendix C for these studies.

Detailed information regarding the collection, handling, and shipment of PK assessment samples is provided in the 015001 Central Laboratory Manual.

8.3.7 Immunogenicity Assessments

Both humoral and cellular immune responses to JCAR015 will be assessed. Humoral responses will be evaluated by testing serum in an ATA assay in which binding to the extracellular region of JCAR015 is measured. The assay for humoral immunogenicity will be a cell-based assay, detecting antibodies that bind to a Jurkat cell line transfected with the JCAR015 construct. This cell line stably expresses the complete JCAR015 sequence and can be used to detect antibodies that bind to any epitope on the extracellular domain of the protein. Cellular responses to JCAR015 will be evaluated by stimulating PBMC with overlapping peptides from JCAR015 and measuring the CTL response by ELISpot. Peripheral blood will be collected for these studies at timepoints indicated in Table C-1 in Appendix C.

Detailed information regarding the collection, handling, and shipment of immunogenicity assessment samples is provided in the 015001 Central Laboratory Manual.

8.3.8 Biomarker Evaluations

Biomarker evaluations will include immunophenotypic characterization of JCAR015 and leukemic cells, enumeration of immune cell subsets, quantitation of CD19 and CD22 on leukemic blasts, RNA expression analysis, and serum cytokines associated with CRS and immune cell function. DNA sequencing will be performed in subjects who consent to this analysis to further characterize leukemic cells for correlation with response to treatment. Peripheral blood, bone marrow aspirates, and CSF will be collected for these evaluations at the timepoints indicated in Appendix C. Instances where specimens are not collected at the required study visit due to insufficient sample volume or subject refusal will not be reported as a protocol deviation.

IgH sequencing will be used to determine whether JCAR015 eliminates all detectable malignant clones, or whether a particular clonal variant is resistant to JCAR015. Additionally, this method may provide information about the clonal evolution of IgH sequences on leukemic cells. MRD analysis will utilize a central laboratory IgH sequencing assay with a level of detection of 10^{-6} (0.0001%).

Flow cytometry will be used to determine the phenotype of JCAR015 cells and enumerate immune cell subsets to identify cellular markers correlated with JCAR015 persistence as well as safety and efficacy. Immunogenicity studies that monitor humoral and cellular immune responses to JCAR015 will be correlated with JCAR015 persistence and efficacy. Quantification of CD19 on leukemic blasts allows assessment of the relationship between tumor target expression and efficacy and safety. Loss of CD19 expression has been associated with relapse in some patients treated with CD19-targeted CARs. CD22 has a B-cell distribution pattern similar to CD19 and can be present on CD19-negative blasts. CD22 will be quantified on leukemic blasts at screening and at relapse to assess the relationship between CD22 and CD19 expression as it relates to efficacy, duration of response, and relapse. Serum cytokines will be measured as a marker of immune activation. Potential correlations between cytokine production and efficacy and severity of CRS will be assessed. Single nucleotide polymorphism (SNP), targeted mutational analysis, whole exome/genome sequencing, and/or gene expression analysis (e.g., RNA-Seq) may be conducted

on JCAR015 cells pre-infusion, or isolated from peripheral blood and bone marrow aspirates post-infusion, along with leukemic cells, in order to identify markers or signatures correlating with response, duration of response, and/or severity of CRS. Assessment of specific cellular elements within the tumor microenvironment (bone marrow) will be performed in order to correlate the presence of these factors with remission, duration of response and/or JCAR015 persistence and function.

Bone marrow core biopsy specimens will be collected for immunohistochemical evaluation of co-inhibitory and co-stimulatory molecules expressed on bone marrow cells, and their respective ligands on leukemic cells. Co-inhibitory and co-stimulatory interactions on T cells and leukemic cells, and immunoregulatory pathways, may influence the fate and function of adoptively transferred CAR T cells. These data, used in combination with the genetic and immunophenotyping assessments, may provide added insights into the spatial relationships between receptors and their respective ligands in the tumor microenvironment.

Testing and analysis of the samples will generally follow the schedule of events in Appendix C. 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 protocol.

8.3.9 Patient-Reported Outcomes and Hospital Resource Utilization

Patient-reported quality-of-life outcomes will be administered according to Appendix B at Part B screening, at Day 28, and again at Month 3, 6, 9, and 12. If the subject withdraws from the study prematurely, all attempts should be made to obtain a final quality-of-life questionnaire prior to subject discontinuation. The FACT-Leu, version 4 questionnaire (Cella 2012) will be used to assess the subject's health as well as physical, social, emotional, and functional well-being.

The questionnaire will be completed by the subjects before any clinical assessments are performed at any given visit. If subjects refuse to complete all or any part of a questionnaire, this will be documented in the CRF. Questionnaires should be completed in the language most familiar to them, and subjects should be given adequate time and space to complete the questionnaire. Site personnel should review questionnaires for completeness and ask subjects to complete any missing responses.

Hospital resource utilization will be assessed based on the numbers of ICU inpatient days and non-ICU inpatient days. Dates of admission and discharge to the hospital and to the ICU will be collected on the appropriate CRF.

9 SAFETY MONITORING AND REPORTING

9.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study subject, which does not necessarily have a causal relationship with this treatment (i.e., JCAR015). An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (i.e., JCAR015).

Adverse events that start or worsen after informed consent and prior to lymphodepleting therapy will not be recorded in the AE section of the CRF unless they are serious AEs. Adverse events and clinically significant abnormal laboratory findings (see Section 9.1.3) that begin or worsen in Part B after the first dose of lymphodepleting chemotherapy, including observed or suspected problems, complaints, or symptoms, will be collected and recorded on the appropriate CRF. From the start of lymphodepleting chemotherapy in Part B through 30 days after the final JCAR015 infusion, each AE with a change in toxicity grade will be recorded in the CRF as a separate AE record. From 31 to 90 days following the final JCAR015 infusion, AEs with changes in toxicity grade will be recorded as a single event with the highest toxicity grade experienced at any time during the event recorded. From 91 days after the final JCAR015 infusion to the EOS visit, only related AEs will be collected; changes in toxicity grade will be recorded as a single event with the highest toxicity grade experienced at any time during the event recorded. Documentation must be supported by an entry in the subject's source document. Each AE is to be evaluated for duration, severity, and causal relationship with JCAR015 or other factors.

Whenever possible, AEs should be recorded as a diagnosis (i.e., a specific disease or syndrome) rather than listing individual associated signs and symptoms. If an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. In addition to recording CRS as a diagnosis, the signs and symptoms of CRS and of neurotoxicity will be recorded on separate CRFs.

Any medical condition already present at Part B screening should not be reported as an AE unless the medical condition increases in severity or seriousness after starting lymphodepleting chemotherapy. In this case, it should be reported as an AE and indicated as a worsening event.

It should be noted that a number of JCAR015 subjects may require multiple days of inpatient and/or ICU admission to manage side effects primarily due to sCRS, although there may be some contribution from the antecedent lymphodepleting chemotherapy (i.e., febrile neutropenia). As noted above, sCRS is an expected, 'on-target' effect resulting from the JCAR015 cell expansion and cell activation.

Inpatient or ICU stays, while anticipated, are not scheduled protocol-defined visits. In addition, inpatient or ICU admissions can generate large amounts of clinical data (e.g., multiple concomitant medications, frequent concomitant medication dose changes, laboratory values, and vital sign assessments). Therefore, targeted collection of data from inpatient or ICU stays, as well as a separate CRF for detailing specific AESI (i.e., signs and symptoms of CRS and neurotoxicity), will be utilized for the purpose of adequately describing the expected risks of JCAR015 and the recommendations for managing these risks.

9.1.1 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product).

9.1.2 Grading and Intensity of Adverse Events

The severity of each AE will be graded using the CTCAE version 4.03 grading criteria (http://ctep.cancer.gov/reporting/ctc.html). If CTCAE criteria do not exist for a given event, the Investigator should use one of the following: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with CTCAE, these intensity grades are defined below:

- Grade 1: Mild – An event that is usually transient in nature and generally not interfering with activities, the AE is generally easily tolerated, does not require treatment.
- Grade 2: Moderate – An event that produces discomfort sufficient to interfere with some aspect of the subject's usual activity and may require medical intervention.
- Grade 3: Severe – An event that results in discomfort or disability which is incapacitating and preventing most normal daily activities and requires medical intervention and/or close follow up.
- Grade 4: Life-threatening – An event that could reasonably result in a potential threat to life.
- Grade 5: Fatal – The AE results in death.

9.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings should be recorded as AEs as per Section 9.1. Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs (see details for assessing clinical significance in Section 8.3.5.1).

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) and other abnormal assessments (e.g., ECG or vital signs) that require medical or surgical intervention, lead to product discontinuation, or are associated with signs and/or symptoms must be recorded as an AE or SAE. The severity of each laboratory abnormality will be graded using the CTCAE version 4.03 grading criteria. If the laboratory abnormality is part of a syndrome (CRS, e.g.), the syndrome or diagnosis (e.g., anemia), and not the laboratory result (i.e., decreased hemoglobin), should be recorded.

Clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

9.1.4 Relationship to Study Drug

The assessment of the relationship of an AE to the administration of lymphodepleting chemotherapy and JCAR015 (related or not related) is a clinical decision based on all available information and the following considerations:

- No (not related):

  The time course between administration of study therapy (JCAR015 administration, e.g.) and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

- Yes (related):

  The time course between administration of study therapy (JCAR015 administration, e.g.) and the occurrence or worsening of the AE is consistent with a causal relationship.

The following factors should also be considered:

- Temporal sequence from study therapy administration

  Event should occur after study therapy is administered. The length of time from study therapy exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant medication

  Other drugs/therapies the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of drug

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses

  Exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- Pharmacology of the test therapy

  Known properties (i.e., in vivo cellular expression) of the test therapy should be considered.

9.2 Serious Adverse Events

An SAE is defined as an event that, at any dose:

- Results in death;
- Is life-threatening;

  NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of an existing hospitalization;

  NOTE: The following hospitalizations will not be considered SAEs: (1) admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits), (2) hospitalization at the discretion of the Investigator for administration of JCAR015 or for ease of clinical monitoring, and (3) hospitalizations for elective or pre-planned treatment for a pre-existing condition that is unrelated to the condition under study and has not worsened since signing informed consent.

- Results in a disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

  NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are other invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency, or drug abuse.

9.2.1 Serious Adverse Event Reporting

Serious adverse events will be reported by Juno Therapeutics to the US FDA and to the NIH Office of Biotechnology Biosafety Program within the appropriate reporting timelines in accordance with Federal Regulations (i.e., 21 CFR §312.32) and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (National Institutes of Health 2013), respectively.

All SAEs occurring from the time of initial informed consent until 30 days following the final infusion of JCAR015 must be reported to Juno Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day post-infusion timeline, only SAEs considered related to JCAR015 must be reported to Juno Therapeutics.

To report the SAEs, site personnel will complete an SAE form and submit any supporting documentation (e.g., hospital discharge summary, test results, or autopsy report) within 24 hours of awareness. The SAE report form and/or supporting documentation should be sent via email or fax to the SAE call center (at

Subjects may be emergently treated at any institution. The Investigator will be requested to supply detailed information regarding the event and copies of emergency department/hospital records. Serious adverse events must also be reported to the reviewing IRB/IEC per IRB/IEC requirements, and a copy of that report must be retained at the site and filed in the study files in accordance with the requirements of that institution.

9.2.2 Follow-up of Serious Adverse Events

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must submit a follow-up SAE report form and/or supporting documentation per the procedures outlined above and in the CRF guidelines.

9.2.3 Suspected Unexpected Serious Adverse Reactions

The Sponsor (or a Sponsor-designated vendor) will send copies of expedited reports for all SAEs that are unexpected and related to the study treatment to all concerned regulatory authorities and active Investigator(s) in accordance with local and site-specific requirements. Sites will submit copies of these documents to their IRB/IEC in accordance with the requirements of their institution.

9.2.4 Death Reports

Death is an expected outcome during this study due to the nature of the disease being treated. All deaths must be reported on the Death CRF. Deaths due to disease progression will not be reported as an SAE unless considered related to JCAR015. Any AEs leading to death from the time the subject provides informed consent through 30 days after the final JCAR015 infusion should be reported as an SAE (Section 9.2.1).

Deaths that occur more than 30 days after the final JCAR015 infusion will be captured on the Death CRF and reported as an SAE only if considered related to JCAR015.

During the informed consent process, subjects should be asked to consent to an autopsy to be performed at the time of death. For subjects who consent to an autopsy, autopsy reports will be requested in the event of death. Autopsy reports should be uploaded into the electronic data capture (EDC) system.

9.3 Study Termination

Criteria for pausing or terminating the study are presented in Section 4.3.1. If the study is paused for any of the safety reasons listed in Section 4.3.1, the Investigator(s) and members of the study team will meet in person or by teleconference within 24 hours of the event to have a thorough discussion of the event. Meeting minutes capturing the review of any ongoing investigations, including next steps in the management of the subject and any proposed changes to the protocol will be forwarded to the DSMB by the Juno Medical Director. If all parties are in agreement as to the event resolution, then the study will be resumed.

If the trial cannot proceed due to unavailability of investigational drug product for the treatment of enrolled subjects, Juno will notify the Principal Investigators and will communicate a plan, including timing, for resumption of JCAR015 supply.

9.4 Pregnancy

To ensure subject safety, each pregnancy occurring in a female subject or in the female partner of a male study subject while the subject is on study must be reported to the Sponsor within 24 hours of learning of its occurrence. If the pregnancy is discovered following initiation of JCAR015 treatment, the pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Pregnancy Report Form and reported to the Sponsor. Pregnancy follow-up should be recorded on the same form and submitted to the Sponsor. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

9.5 Data Safety Monitoring Board

An independent DSMB will review cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. The DSMB, composed of a statistician and select physicians with experience in hematology/oncology and/or T cell therapy, will be assembled under a dedicated charter specifically developed for safety oversight of the study. DSMB members will not be actively involved in the study design, conduct, or subject accrual and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision making.

The DSMB will be convened prior to enrollment of the first subject on the protocol and will meet approximately quarterly throughout the trial and as needed to address any safety issues that may arise. Subject safety will be evaluated as specified in the Data Safety and Monitoring Plan (DSMP) or DSMB charter. The DSMB will provide advice to the Sponsor as outlined in the DSMB charter. After each DSMB meeting, a statement summarizing the outcome of the review will be provided to Juno. If the DSMB recommends continuing the study, no details from the review will be revealed. Juno will provide this statement from the DSMB review to the study investigators for submission to the site's IRB/IEC within approximately 10 working days of receipt of the statement.

9.6 Independent Review Committee

An IRC will be established to review data related to disease response assessments and to determine remission and relapse status on an ongoing basis. The IRC will include at least one hematopathologist and will be contracted by Juno Therapeutics, Inc. The details of the IRC processes and review methods will be described in an IRC charter developed by the IRC in conjunction with Juno Therapeutics, Inc. Clinical management of study subjects will be based upon Investigator assessment. The findings of the IRC will be considered primary for analyses of ORR and other efficacy endpoints.

10 STATISTICAL METHODS

10.1 General Considerations

Data from all clinical sites will be combined for the final analysis. Analysis results will be presented using descriptive statistics. For categorical variables, the number, percentage of each category, and 95% CI on the percentage will be presented. For continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), 95% CI on the mean, median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented. Data collected in the study will be presented as by-subject listings for the appropriate analysis set.

10.2 Analysis Sets

10.2.1 Screened Set

The screened set will include all subjects who have signed informed consent.

10.2.2 Enrolled Set

The enrolled set will include all subjects who are enrolled into Part A and undergo leukapheresis.

10.2.3 Primary Efficacy Analysis Set

The primary efficacy analysis set will include all subjects with morphologic evidence of leukemia, as determined by an IRC, at the time of JCAR015 infusion who receive lymphodepleting chemotherapy with cyclophosphamide alone and at least one dose of JCAR015. The primary efficacy analysis set will be used for the primary analyses of ORR and DOR.

10.2.4 JCAR015-Treated Morphological Disease Analysis Set

The JCAR015-treated morphological disease analysis set will include all subjects with morphologic evidence of leukemia, as determined by the IRC at the time of JCAR015 infusion, who receive at least one dose of JCAR015 (i.e., Part B, Group 1).

10.2.5 JCAR015-Treated Analysis Set

The JCAR015-treated analysis set will include all subjects who receive at least one infusion of JCAR015 in Part B of the study (i.e., Part B, Group 1 and Group 2).

10.2.6 Per Protocol Analysis Set

The per protocol (PP) analysis set represents a subset of the primary efficacy analysis set who are compliant with the major requirements of Part B of the study protocol. Subjects who have a disease other than B-cell ALL at baseline, whose prior therapy does not match with the protocol requirements in terms of number and types of prior therapeutic regimens, or who have missing or incomplete documentation of disease will be excluded from the PP analysis set. Subjects who only receive a single dose of JCAR015 in Group 1 will be included in the PP analysis set. The specific classification of subjects to be included in the PP analysis set will be included in the statistical analysis plan which will be finalized prior to any formal data analyses or the database lock.

10.2.7 Pharmacokinetic Analysis Sets

The PK analysis set includes data from subjects in the JCAR015-treated analysis set who have the necessary baseline and on-study PK measurements to provide interpretable results for the specific parameters of interest.

10.2.8 Biomarker Analysis Sets

The biomarker analysis set includes data from subjects in the JCAR015-treated analysis set who have the necessary baseline and on-study biomarker measurements to provide interpretable results for the specific parameters of interest.

10.3 Planned Analyses

10.3.1 Subject Disposition and Baseline Characteristics

Summaries of subject disposition will be provided for the primary efficacy and JCAR015-treated analysis sets. The number and percentage of subjects who are eligible for Part A of the study but not able to successfully generate a JCAR015 cell product, along with the reason(s) for manufacturing failure, will be summarized based on the screened set. Available demographic and baseline information on such subjects will be listed and summarized.

Descriptive summaries of demographics and baseline characteristics will be presented for the primary efficacy and JCAR015-treated analysis sets. In addition, subjects will be classified as follows:

- By allogeneic HSCT status (no prior HSCT, prior HSCT with full donor chimerism, prior HSCT with partial donor chimerism)
- By prior response status (primary refractory, relapse without prior HSCT, relapse after prior HSCT)

10.3.2 Efficacy Analyses

10.3.2.1 Primary Endpoint

The primary endpoint of the study is ORR, as determined by an IRC. The ORR is defined as the proportion of subjects with a best overall response (BOR) of either CR or CRi. The BOR is the best overall disease response recorded from the time of the final JCAR015 infusion (i.e., Dose #2 for subjects who complete JCAR015 treatment and Dose #1 for subjects who receive only one dose of JCAR015) until the start of another anticancer therapy. Best response will be assigned according to the following order: CR, CRi, no response, or unknown. Subjects with unknown or missing response will be included in the denominators in the calculation of ORR.

The primary efficacy analysis will be performed based on the primary efficacy analysis set by testing the null hypothesis of ORR ≤ 20% against the alternative hypothesis that the ORR > 20% at a 1-sided 2.5% level of significance, powered for ORR = 50%, i.e.,

$$H_0: \text{ORR} \leq 20\% \text{ vs. } H_1: \text{ORR} > 20\%$$

The ORR will be summarized along with the 2-sided 95% exact Clopper-Pearson confidence intervals. The study will be considered successful if the lower bound of the 2-sided 95% confidence interval for ORR is greater than 20% such that the null hypothesis is rejected.

The following sensitivity analyses will be performed:

- ORR based on the PP analysis set using the same analysis method as described above
- ORR assessed by the investigators based on the primary efficacy analysis set

10.3.2.2 Secondary Efficacy Endpoints

Secondary endpoint analyses will be performed to further assess the efficacy of JCAR015 by combining data collected in this protocol together with data from the LTFU protocol, where appropriate. The endpoints listed below will be analyzed as secondary endpoints:

- Duration of remission

  Duration of remission (DOR) is defined as the interval from the first documentation of CR or CRi to the earlier date of relapse or death due to ALL. DOR will be evaluated based on the IRC evaluations for subjects in the primary efficacy analysis set who achieve a CR or CRi.

  In case a subject does not have relapse or death due to ALL prior to data cutoff, DOR will be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event. The censoring reason could be:

  – Ongoing
  – Completed the study
  – Discontinued the study
  – Received a new anticancer therapy (also see below for handling of HSCT)
  – Experienced an event after missing at least two consecutive scheduled disease assessments

  Death due to a reason other than ALL will be considered as a competing risk event to other events of interest (relapse or death due to ALL).

  Because HSCT is an important treatment option in responding subjects, it is appropriate to consider the date of HSCT as the censoring date instead of censoring at the last disease assessment date. However, censoring due to HSCT will overestimate the rate of relapse and may therefore be considered inappropriate for the main analysis when a substantial number of subjects choose to receive HSCT (European Medicines Agency 2010). If a subject underwent an HSCT after achieving a CR or CRi in response to JCAR015, relapse or survival status after HSCT will be collected. In such cases, the date of relapse or death due to ALL after HSCT will be used for the calculation of DOR as a sensitivity analysis.

  Another sensitivity analysis will be performed by censoring death due to reason other than ALL instead of considering it as the competing risk event to other events of interest. The proposed analyses for DOR are:

  – Competing risk analysis and censoring at the time of HSCT

- Competing risk analysis and ignoring HSCT as a censoring event
- Censoring at the last adequate disease assessment and censoring at the time of HSCT
- Censoring at the last adequate disease assessment and ignoring HSCT as a censoring event

The first method (i.e., competing risk analysis and censoring at the time of HSCT) will be considered as the primary analysis for DOR. For the competing risk analyses, the cumulative incidence function (CIF) method will be used to estimate the probability of the event of interest (Cheson 2003, Kim 2007). For the other analyses, the KM method will be used to estimate the median DOR along with 95% CI. The estimated percentage of continual response subjects at 6 months and 12 months will be presented with 95% confidence intervals using the CIF or the KM method.

Duration of molecular remission is defined as the interval from the first documentation of an MRD-negative CR or CRi to the earlier date of molecular relapse (appearance of MRD), morphologic relapse, or death due to ALL. The duration of molecular remission will be analyzed using the same methods as for DOR described above.

- Percentage of subjects who achieve a CR or CRi with no evidence of MRD in the bone marrow (i.e., below the level of detection for the IgH gene sequencing assay)

  The percentage of subjects with an MRD-negative bone marrow at the time of achieving CR or CRi will be summarized along with the exact 95% confidence interval. The analysis will be performed for the primary efficacy and JCAR015-treated analysis sets.

- Relapse-free survival

  Relapse-free survival (RFS) is defined as the interval from the first documentation of CR or CRi to the earlier date of relapse or death due to any cause. RFS will be evaluated based on subjects in the primary efficacy analysis set who achieve a CR or CRi after the final dose of JCAR015.

  In case a subject does not have relapse or death prior to data cutoff, RFS will be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event. The censoring reason could be:

  - Ongoing
  - Completed the study
  - Discontinued the study
  - Received a new anticancer therapy (see also below for handling of HSCT)
  - Experienced an event after missing at least two consecutive scheduled disease assessments

  Subjects who proceed to HSCT after JCAR015 infusion will be censored at the time of HSCT. A sensitivity analysis will be performed without censoring HSCT. KM method will be used to estimate the 6-month RFS rate, 12-month RFS rate, and median RFS along with the 95% CI.

- Event-free survival

Event-free survival (EFS) is defined as the interval from the date of the first JCAR015 infusion to the earliest of the following events: death from any cause, relapse, or treatment failure (defined as no response and subsequent discontinuation from the study for AE, lack of efficacy, or progressive disease, or new anticancer therapy). EFS will be evaluated based on the JCAR015-treated and primary efficacy analysis sets.

In case a subject does not have an EFS event prior to data cutoff, EFS will be censored at the date of the last adequate disease assessment on or prior to the earliest censoring event. The censoring reason could be:

- Ongoing
- Lost to follow-up
- Withdrawal of consent
- Received a new anticancer therapy (also see below for handling of HSCT)
- Experienced an event after missing at least two consecutive scheduled disease assessments

In the case of treatment failure, the event date will be set to study Day 1 (European Medicines Agency 2010).

Subjects who proceed to HSCT after JCAR015 infusion will be censored at the time of HSCT. A sensitivity analysis will be performed without censoring for HSCT. The KM method will be used to estimate the 6-month EFS rate, 12-month EFS rate, and median EFS along with the 95% CI.

- Overall survival

  Overall survival (OS) is defined as the interval from the date of the first JCAR015 infusion to the date of death due to any reason. Data from surviving subjects will be censored at the last time that the subject is known to be alive. No censoring will be done in the case of HSCT. OS will be evaluated based on the JCAR015-treated and primary efficacy analysis sets.

  The KM method will be used to estimate 6-month OS rate, 12-month OS rate, and median OS along with the 95% CI.

- Percentage of subjects who achieve a CR or CRi at Month 6 without HSCT from the time of the final JCAR015 infusion to the Month 6 post-infusion assessment

  The percentage of subjects in the primary efficacy analysis set who achieve a CR or CRi without HSCT between the final JCAR015 infusion and the Month 6 response assessment will be summarized along with the exact 95% confidence interval. The time of proceeding to HSCT is defined as the time of commencing the conditioning regimen as required for HSCT.

- Percentage of subjects who achieve a CR or CRi and then proceed to HSCT while in remission within 6 months after the final JCAR015 infusion

  The percentage of subjects in the primary efficacy analysis set who achieve a CR or CRi following the final JCAR015 infusion and then proceed to HSCT while in remission by the

Month 6 response assessment will be summarized along with the exact 95% confidence interval. The time of proceeding to HSCT is defined as the time of commencing the conditioning regimen as required for HSCT.

10.3.2.3 Efficacy Subgroup Analysis

Subgroup analysis will be performed on the following variables based on the subject's baseline status:

- Age: < 40, ≥ 40 to < 65, ≥ 65 years at the time of the first JCAR015 infusion
- Prior response status: refractory, relapse without transplant, relapse after transplant
- Philadelphia chromosome status: positive versus negative
- Prior HSCT Status: yes versus no
- Number of relapses prior to first JCAR015 infusion: one relapse versus two or more relapses
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: white versus non-white

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

10.3.3 Safety Analyses

Safety data will be summarized for the JCAR015-treated analysis set.

10.3.3.1 Adverse Events

All AEs will be listed. The focus of AE summarization will be on JCAR015 treatment-emergent AEs. A JCAR015 treatment-emergent AE (TEAE) is defined as an AE that occurs or worsens after the first JCAR015 infusion and within 30 days after the final JCAR015 infusion, or an AE leading to JCAR015 discontinuation. Any AE occurring after the initiation of another anticancer therapy will not be considered a JCAR015 TEAE.

Reporting of AEs will be based on the Medical Dictionary for Regulatory Activities (MedDRA) and CTCAE version 4.03. TEAEs will be summarized by system organ class (SOC), preferred term, and severity. A subject who reports multiple occurrence of TEAEs within the same SOC and preferred term is counted only once using the maximum severity grade for summaries. In addition, TEAEs that occur after the first (but prior to second) JCAR015 infusion, and TEAEs that occur after the second JCAR015 infusion will be summarized separately. Listings and summaries will be prepared for the following type of TEAEs:

- Serious AEs
- Grade 3 or higher AEs
- JCAR015-related AEs
- AEs leading to JCAR015 discontinuation

- AEs leading to study discontinuation
- AEs leading to death

10.3.3.2 Adverse Events of Special Interest

The following AEs are considered to be AESI:

- **Syndromes** including the following MedDRA preferred terms: cytokine release syndrome, histiocytosis haematophagic, and tumour lysis syndrome
- **CRS symptoms** including the following MedDRA preferred terms: pyrexia, myalgia, hypotension, dyspnoea, tachypnoea, capillary leak syndrome, hypoxia, organ failure, and acute respiratory distress syndrome
- **Neurological toxicity** including the following MedDRA preferred terms: mental status changes, delirium, confusional state, disorientation, aphasia, seizure, seizure-like phenomena, encephalopathy, tremor, myoclonus, lethargy, and depressed level of consciousness
- **Macrophage activation syndrome** including the following MedDRA preferred terms: hepatosplenomegaly, lymphadenopathy, pancytopenia, disseminated intravascular coagulation, hypertriglyceridaemia, hyperferritinaemia, hypofibrinogenaemia, pyrexia, hepatic enzyme increased, hyponatraemia, prothrombin time prolonged, activated partial thromboplastin time prolonged, and fibrin degradation products increased
- **TLS** including the following MedDRA preferred terms: hyperkalaemia, hyperphosphataemia, hyperuricaemia, and hypocalcaemia
- **HLH** symptoms including the following MedDRA preferred terms: splenomegaly, haemolysis, disseminated intravascular coagulation, blood triglycerides increased, and serum ferritin increased; and including a MedDRA high level term: marrow depression and hypoplastic anaemias
- **Organ dysfunction** including the following MedDRA high level terms: hepatic enzymes and function abnormalities, renal failure and impairment, and confusion and disorientation
- **Allergic reaction** using the MedDRA preferred term of infusion-related reaction

The search terms of the AESI may be updated prior to reporting. Treatment-emergent AESI will be summarized by group term and search terms. Time to onset and resolution of first event will be summarized.

10.3.3.3 Laboratory Data

All laboratory data will be listed. The focus of laboratory data summarization (including hematology, serum chemistry, and selected immunoglobulin parameters) will be on JCAR015-treatment-emergent laboratory abnormalities. A JCAR015 treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by at least one grade after the first JCAR015 infusion and up to 30 days after the final JCAR015 infusion. The baseline value is defined as the last available recorded value on or prior to the date of the first dose of JCAR015.

If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent. Hematological and serum biochemistry data will be programmatically graded according to CTCAE version 4.03, when applicable. Grade 0 includes all non-missing 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 (i.e., increased, decreased) will be presented separately.

The following summaries will be presented for selected analyte:

- Raw values and changes from baseline will be summarized by visit for numerical lab results in conventional units
- Number of subjects by CTCAE severity grade, with corresponding percentages at each visit, and maximum post-baseline severity grade
- Shift tables showing the change in CTCAE severity grade from baseline to the maximum severity grade post baseline; for laboratory tests where CTCAE grade does not exist, the shift table will present the low/normal/high shift

10.3.3.4 Immunogenicity Data

Humoral immunogenicity assessment will include prevalence of immunogenicity (subjects with pre-existing antibodies that bind to JCAR015), incidence of immunogenicity (subjects with treatment-induced or treatment-boosted antibodies that bind to JCAR015), together with antibody titres. Data will be further fractionated to determine proportion of subjects who make transient versus sustained antibody responses. Cellular immunogenicity assessment will include percentage of CD4+ and CD8+ T cells specific for JCAR015.

10.3.3.5 Other Safety Data

Vital signs and ECG data will be summarized using descriptive statistics and listed. The MMSE total score change from baseline at each timepoint will be summarized. All other safety data will be listed.

10.3.3.6 Concomitant Medications

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary (WHO-DD) and listed. All concomitant medications and blood product transfusions administered after first dose of JCAR015 will be summarized.

Specific treatments for CRS (i.e., corticosteroids, tocilizumab) will be summarized. As an exploratory analysis, response status and time to response of sCRS to interventions (e.g., time to fever reduction after treatment and proportion of subjects who respond to intervention within 24 hours based on grade) will be presented.

10.3.3.7 Safety Subgroup Analysis

Subgroup analysis will be performed for key safety summaries based on the following variables:

- Disease burden: morphologic disease at the time of JCAR015 treatment (i.e., Group 1) versus no morphologic disease at the time of JCAR015 treatment (i.e., Group 2)

- Age: < 40, ≥ 40 to < 65, ≥ 65 years at the time of the first JCAR015 infusion
- Prior response status: refractory, relapse without transplant, relapse after transplant
- Philadelphia chromosome status: positive versus negative
- Prior HSCT Status: yes versus no
- Number of relapses prior to first JCAR015 infusion: one relapse versus two or more relapses
- Sex: male versus female
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: White versus Non-White
- Lymphodepleting chemotherapy: cyclophosphamide versus fludarabine + cyclophosphamide

Subgroup analyses will be based on the JCAR015-treated analysis set and will only be performed if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups.

10.3.4 Pharmacokinetic Analysis

Assays for the analysis of various cellular PK parameters include a qPCR assay to detect JCAR015 cells (transgene copies/microgram of DNA) in peripheral blood and bone marrow, as well as flow cytometry analysis to detect JCAR015 cells in peripheral blood and bone marrow. Other tissues (e.g., cerebrospinal fluid) may be analyzed for presence of JCAR015 cells using the qPCR and flow cytometry assays. Details of the sample collection procedures for these assays are provided in the 015001 Central Laboratory Manual.

The assessment of JCAR015 cellular PK will measure the percent of PBMCs and bone marrow mononuclear cells expressing the JCAR015 transgene, and when the appropriate detection reagent becomes available, the relative percent of T cell subsets that express the JCAR015 transgene protein.

For all subjects treated with JCAR015, the in vivo PK profile of JCAR015 cells in target tissues (blood, bone marrow, and CSF) will be characterized, including C_{max}, T_{max}, AUC, and other relevant PK parameters. The maximum extent of expansion of JCAR015 in the blood will be determined ($C_{max}/C_{post\text{-}dose\ Day\ 2}$), along with the persistence of JCAR015 in the blood and bone marrow, based on both the qPCR assay (time above lower limit of quantification) and flow cytometry assay (time above threshold JCAR015 level).

The following PK parameters will be displayed graphically where possible: qPCR-based JCAR015 concentration versus time in peripheral blood, bone marrow, and CSF; flow cytometry-based JCAR015 concentration versus time in peripheral blood, bone marrow, and CSF.

The following PK parameters, along with other relevant PK parameters, will be estimated from the individual concentration-time profiles using a non-compartmental analysis approach: $AUC_{0\text{-}Tmax}$, $AUC_{Tmax\text{-}56d}$, C_{max}, T_{max}, $T_{1/2}$, $C_{max}/C_{post\text{-}dose\ Day\ 2}$, and time above lower limit of quantification. All concentrations below the limit of detection or quantitation, or missing data,

will be labeled as such in the concentration data listings. Concentrations below the limit of detection will be treated as zero in summary statistics.

Descriptive statistics for PK parameters will be categorized by clinical response and will include mean, standard deviation, coefficient of variation, minimum, and maximum. Ranges of values may be presented for selected variables. Median values and ranges will be used for T_{max} as it is typically evaluated by a non-parametric method.

Finally, the relationship between the use of steroids, occurrence of immunogenicity, and other relevant covariates and cellular PK will be explored.

10.3.4.1 Pharmacokinetic Subgroup Analysis

Subgroup analyses will be performed for key PK summaries based on the following variables:

- Disease burden: morphologic disease at the time of JCAR015 treatment (i.e., Group 1) versus no morphologic disease at the time of JCAR015 treatment (i.e., Group 2)
- Sex: male versus female
- Cellular and/or humoral immunogenicity: present (positive) or absent (negative)
- Ethnicity: Hispanic or Latino versus not Hispanic or Latino
- Race: white versus non-white
- Lymphodepleting chemotherapy: cyclophosphamide versus fludarabine + cyclophosphamide

Subgroup analyses will be based on the JCAR015-treated analysis set and will only be performed if there are at least five subjects in each subgroup. Some grouping of classes will be considered if there are too few subjects in some subgroups.

10.3.5 Biomarker Analyses

The study sample size is not powered for biomarker analyses; therefore, all biomarker analyses will be exploratory in nature. There may be circumstances where a decision is made to stop biomarker sample collection, or not perform or discontinue the analysis of blood or bone marrow due to either practical or sample quality reasons. In such circumstances, the number of samples may be insufficient to perform a complete data analysis, and as such, the available data will be listed and summarized.

Additional analyses that may be performed after the completion of the clinical study report (CSR) will be documented in separate reports. These analyses may include, but are not limited to, cross-study analyses of data from this study combined with data from other studies, or the analysis of biomarker data generated from samples collected during the study but analyzed after database lock and completion of the CSR. Any such data analysis will be described in an addendum to the CSR or in a stand-alone report, as appropriate.

Malignant and normal B cell populations will be listed and summarized by subject and visit. Absolute and relative change (percent change) from baseline will be summarized using descriptive statistics. Subject level and average cell counts and percent change from baseline may be plotted over time.

The clonal distribution of leukemic cells, as measured by IgH deep sequencing, will be listed per subject and percent change from baseline will be summarized using descriptive statistics. Subject level absolute and relative changes may be plotted over time.

Soluble inflammatory markers and serum cytokines (e.g., IL-10, IFNγ, IL-6, IL-6R, CRP, and ferritin) will be listed and summarized by subject and visit. Serum cytokine data will be log-transformed for statistical analyses. Absolute and relative change (percent and or fold change) from baseline will be calculated for each visit using descriptive summaries. The maximum change from baseline measure for each cytokine may also be graphed against clinical response status and severity of CRS response using strip plots. Subject level and averaged cytokine measures and percent change from baseline may be displayed using longitudinal plots.

CD8- and CD4-positive JCAR015 T cells will be listed and summarized by timepoint if a JCAR015 protein detection reagent becomes available; the number of JCAR015-positive cells in subjects will also be listed and summarized by timepoint. Data will also be summarized by response status and potentially graphed using strip plots. Subject level and average longitudinal plots of the cell counts and percent changes from baseline may be generated.

10.3.6 JCAR015 Product Quality Attributes and Process Performance Attributes

Selected clinical and safety endpoints will be summarized descriptively by JCAR015 product characteristics (e.g., T cell subsets, transduction efficiency, in vivo expansion potential, and vector copy number).

10.3.7 Exploratory Analyses

10.3.7.1 Peripheral Blood B Cell Count

Peripheral blood will be analyzed at study assessment timepoints for the number of non-malignant B cells, leukemic blasts, CAR^+ T cells, and T cell subset distribution, and recovery of normal B cells or disappearance of CAR^+ T cells, whichever occurs later.

10.3.7.2 Severe Cytokine Release Syndrome

Severe CRS is defined as Grade 3 or higher CRS based on the protocol-specified grading scale (see Section 7.1). Time to the occurrence of first sCRS and duration of sCRS will be summarized. Changes in inflammatory markers (including CRP and serum ferritin) and cytokines, and the relationship with sCRS will be explored. The relationship of baseline disease burden, clinical response, and PK/PD parameters may also be explored. Data regarding the severity of CRS and response to anti-cytokine therapy will be listed and summarized.

10.3.7.3 Leukemia Gene Expression Profiling and Genomic Analysis

The relationship between pre-treatment leukemia genomic analysis (i.e., gene expression profiles, mutational analysis from targeted or whole exome/genome sequencing) and selected clinical outcomes (e.g., JCAR015 efficacy, safety, cellular PK) will be explored. Selected gene expression profiles will be summarized descriptively by subject outcome. Analysis of genomic changes between pre-treatment leukemia samples and samples obtained following JCAR015 infusion, and at relapse (if available), will be summarized descriptively by subject outcome.

Gene expression profiling (e.g., RNA-Seq) will be performed on host immune cell subsets obtained from peripheral blood. Analysis of RNA expression changes between pre-treatment samples and post-treatment samples will be summarized descriptively by subject outcome.

10.3.7.4 JCAR015 Gene Expression Profiling

Gene expression profiling (e.g., RNA-Seq) will be performed on JCAR015 cells obtained at the end of manufacturing and from peripheral blood post-infusion. Analysis of RNA expression changes between end-of-manufacturing samples and post-treatment samples will be summarized descriptively by subject outcome.

10.3.7.5 Patient-Reported Outcomes and Hospital Resource Utilization

The FACT-Leu questionnaire data will be scored, processed, and standardized according to the user manual. Missing items in a subscale will be imputed according to the user manual instructions. Data collected from the FACT-Leu instrument will not be reconciled with AE or laboratory data. The mean and change from baseline in mean scores to each subsequent assessment will be summarized for the FACT-Leu subscale and composite (i.e., total outcome index, FACT-G total, and FACT-Leu total) scores. The analyses will be based on the JCAR015-treated morphological disease and JCAR015-treated analysis sets.

Hospital resource utilization will be listed and summarized. The relationship between treatment setting (i.e., inpatient, outpatient, ICU) and selected subgroups (e.g., subjects with morphologic disease, subjects with MRD) will be explored. Hospital resource utilization for subjects with AESI will be listed and summarized.

10.4 Sample Size Considerations

In a previous Phase 2 study of vincristine sulfate liposomal injection (HBS407) in adult subjects with Ph-negative ALL in second or greater relapse, the ORR (CR + CRi as determined by an IRC) was 15.4%. Based on the null hypothesis of ORR $\leq$ 20% and an alternative hypothesis of ORR=50%, 50 subjects in the primary efficacy analysis set will provide > 95% power to demonstrate statistical significance at a 1-sided 0.025 significance level and will provide an ample safety database.

An interim analysis is planned based on approximately ten subjects in the JCAR15-treated morphological disease analysis set. This interim analysis will assess analytical and clinical comparability between the JCAR015 cell product used in this study and the 1928z CAR T-cell product used in the ongoing Phase 1 study (MSKCC Protocol 09-114).

Assuming that 15% of subjects enrolled on Part A will not be infused with JCAR015 due to reasons such as manufacturing failure or worsening of subject's medical condition and 25% of subjects enrolled on Part A will achieve a CR from cytoreductive chemotherapy and be treated in Group 2 of Part B, approximately 110 subjects need to be enrolled to ensure that a minimum of 50 subjects are in the primary efficacy analysis set.

10.5 Timing of Analyses

10.5.1 Interim Analysis

Efficacy monitoring boundaries based on the posterior probability of ORR will be implemented to continuously monitor the efficacy data in the JCAR015-treated morphological disease analysis set during the course of this study. The ORR for the purpose of this analysis will be based on Investigator assessment. Whenever the boundary is crossed, an ad hoc DSMB meeting will be held to review the study data, and an enrollment pause may be triggered pending the DSMB's recommendations. The boundaries are constructed for the purpose of efficacy monitoring and will not be used to stop the trial early for positive outcome. Details regarding the efficacy monitoring boundaries are included in the statistical analysis plan.

A formal interim analysis is planned after approximately ten Group 1 (JCAR015-treated morphological disease) subjects are treated and are followed for at least 1 month after the final JCAR015 infusion.

In addition to safety and efficacy assessments, this interim analysis will assess the comparability between the JCAR015 cell product used in this study and the 1928z CAR T cell product used in the ongoing Phase 1 study (MSKCC Protocol 09-114). In addition to ten Group 1 (JCAR015-treated morphological disease) subjects, it is estimated that approximately four additional subjects will achieve a CR from the cytoreductive chemotherapy administered in Part A. These subjects would be assigned to Group 2 and will receive JCAR015. TEAEs and AESI will be summarized for all JCAR015-treated subjects at the time the interim analysis is performed. Safety data from a cohort of subjects with similar baseline characteristics and who receive a similar CAR^+ T cell dose on MSKCC Protocol 09-114 will be summarized. The assessment of comparability will be descriptive and will not involve inferential statistics.

10.5.2 Primary Analyses

The primary analyses will be carried out after all subjects in the JCAR015-treated morphological disease analysis set are followed for at least 6 months from the start of Part B or have discontinued the study due to any reason.

10.5.3 Final Analyses

The final analyses will be carried out after all subjects have completed or discontinued the study due to any reason.

11 DATA MANAGEMENT

11.1 Data Collection System

An EDC system provided by Juno Therapeutics 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; 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. A Juno Therapeutics 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 non-conformant data during data entry. Data review by the Juno Therapeutics 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 CRF 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 Approval

The study will be conducted in accordance with Good Clinical Practice (GCP), the protocol, and any other applicable regulatory requirements by the FDA.

12.1.2 Institutional Review Board/Independent Ethics Committee Approval

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

If the protocol or the ICF is amended during the study, per local regulations, the Investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. In addition, IRB/IEC 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

JCAR015 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 (i.e., leukapheresis cell product) nor the final investigational drug product has been tested for the presence of communicable diseases in accordance with the provisions in 21 CFR §1271.90(a)(1), the JCAR015 investigational drug product should be handled according to institutional procedures and OSHA Universal Precautions for materials that may contain infectious agents (e.g., 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 and any other required materials prior to initiating the study if required per institutional policy and in accordance with local procedures and country-specific regulatory requirements. If applicable, documentation of IBC approval must be in place prior to product 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, the 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/IEC-approved consent form for documenting written informed consent. Each ICF 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 IRB or IEC or local requirements. The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference of Harmonization (ICH) requirements (ICH E6 4.8), 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/IEC. 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 subinvestigators 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, subinvestigators, and study staff 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 subinvestigators') participation in the study. The Investigator and subinvestigator agree to notify Juno Therapeutics of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the study database is locked.

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

The Investigator will sign and return to Juno the "Protocol Signature Page" of the original protocol and any protocol amendment, 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/IEC of the progress of the study and to notify the IRB/IEC of study closure. The Investigator must also provide Juno with copies of all IRB/IEC correspondence that relates to study approvals, updates, or changes. The Investigator must also forward all IRB/IEC renewals to Juno.

12.3 Access to Information for Monitoring

In accordance with regulations and guidelines, the designated Juno CRA must have direct access to the Investigator's source documentation in order to verify the accuracy of the data recorded in the CRF.

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, Juno Therapeutics, or the IRB/IEC 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 Medical Director immediately. The Investigator agrees to provide to representatives of a regulatory agency or Juno access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12.5 Quality Control

Juno 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, Juno personnel will provide training as needed to the Investigator, subinvestigators, and study site personnel regarding the following: protocol, IB, CRFs and procedures for their completion, informed consent process, and procedures for reporting SAEs. Site visits will be performed by Juno CRAs or designees periodically throughout the study. During these visits, information recorded on the CRFs will be verified against source documents, and requests for clarification or correction may be made. The CRFs 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.

A DSMB will review safety data (e.g., AEs and SAEs, laboratory data, and production data) approximately quarterly as the clinical trial is ongoing.

12.6 Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) 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.

12.7 Study Termination

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 non-electronic study data (e.g., copies of ECG tracings) to Juno, if requested;
- Data clarifications and/or resolutions;

- Accounting, reconciliation, and final disposition of used and unused investigational product; and
- Review of site study records for completeness.

Juno reserves the right to temporarily suspend or prematurely terminate this study for any reason. If the study is suspended or terminated for safety reasons, Juno 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 is responsible for promptly informing the IRB/IEC and providing the reasons for the suspension or termination of the study.

12.8 Site Termination

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

12.9 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 investigational product, regulatory documents, and other Juno Therapeutics 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 must be notified in writing and given the opportunity to further store such records.

12.10 Confidentiality of Information

Subjects' names will remain confidential and will not be included in the database. All study findings will be stored in electronic databases. The Investigator will maintain a personal subject identification list (subject and treatment numbers with the corresponding subject names) to enable records to be identified.

The Investigator agrees that all information received from Juno, including, but not limited to, the JCAR015 product IB, this protocol, CRFs, and any other study information, remain the sole and exclusive property of Juno Therapeutics during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Juno. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

12.11 Publication Plan

Juno is responsible for the 015001 final CSR which will be prepared according to ICH guidelines. The final CSR will include data from any subject who has signed informed consent, regardless of

whether the study is completed or prematurely terminated. If appropriate, an abbreviated report may be written. The CSR will be written in English and will be in compliance with any applicable regulatory requirements and national laws.

All unpublished information given to the Investigator by Juno shall not be published or disclosed to any third party without the prior written consent of Juno. As Juno generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be sent to Investigators for comments and suggestions. Endorsement of the final CSR may be sought from Investigators when required by local regulatory agencies.

No patent application(s) based on study results may be made by the Investigator nor may assistance be given to any third party to make such an application without the written authorization of Juno. Neither the Investigators nor anyone else working on the study may submit any publications, papers, abstracts, or other written materials or oral presentations related to the study without express written consent from Juno Therapeutics, Inc.

13 CONTACT INFORMATION

13.1 Study Sponsor

Juno Therapeutics, Inc.
307 Westlake Ave North,
Seattle, WA 98109
Phone:
www.junotherapeutics.com

13.2 Global Drug Safety

13.3 Manufacturing Facility

14 REFERENCES

1. Amadori S, Arcese W, Isacchi G, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. J Clin Oncol 1991;9(7):1210-1214.
2. Bassan R and Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 2011;29(5):532-543.
3. Bassan R, Lerede T and Barbui T. Strategies for the treatment of recurrent acute lymphoblastic leukemia in adults. Haematologica 1996;81(1):20-36.
4. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 2013;5(177):177ra138.
5. 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):4817-4828.
6. Brentjens RJ, Santos E, Nikhamin Y, et al. Genetically targeted T cells eradicate systemic acute lymphoblastic leukemia xenografts. Clin Cancer Res 2007;13(18 Pt 1):5426-5435.
7. Cairo MS and Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127(1):3-11.
8. Cella D, Jensen SE, Webster K, et al. Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy--Leukemia (FACT-Leu) questionnaire. Value Health 2012;15(8):1051-1058.
9. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21(24):4642-4649.
10. Cruz CR, Hanley PJ, Liu H, et al. Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience. Cytotherapy 2010;12(6):743-749.
11. Davila ML, Kloss CC, Gunset G, et al. CD19 CAR-targeted T cells induce long-term remission and B Cell Aplasia in an immunocompetent mouse model of B cell acute lymphoblastic leukemia. PLoS One 2013;8(4):e61338.
12. 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):224ra225.
13. European Medicines Agency. Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies. 2010.
14. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood 2007;109(3):944-950.
15. Food and Drug Administration. Guidance for Industry: 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. 2000.
16. Garcia-Manero G and Thomas DA. Salvage therapy for refractory or relapsed acute lymphocytic leukemia. Hematol Oncol Clin North Am 2001;15(1):163-205.

17. Gokbuget N and Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Semin Hematol 2009;46(1):64-75.
18. Gokbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood 2012;120(10):2032-2041.
19. Grossman Z, Min B, Meier-Schellersheim M, et al. Concomitant regulation of T-cell activation and homeostasis. Nat Rev Immunol 2004;4(5):387-395.
20. 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.
21. Grupp SA, Maude SL, Shaw PA, et al. T Cells Engineered with a Chimeric Antigen Receptor (CAR) Targeting CD19 (CTL019) Have Long Term Persistence and Induce Durable Remissions in Children with Relapsed, Refractory ALL. 56th Annual Meeting of the American Society of Hematology. 2014; San Francisco, CA.
22. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(2):124-131.
23. Howard SC, Jones DP and Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364(19):1844-1854.
24. Jain N, O'Brien S, Thomas DA, et al. Inotuzumab Ozogamicin In Combination With Low-Intensity Chemotherapy (Mini-hyper-CVD) As Frontline Therapy For Older Patients (≥60 years) With Acute Lymphoblastic Leukemia (ALL). 55th Annual Meeting of the American Society of Hematolgoy. 2013; New Orleans, LA.
25. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci Transl Med 2011;3(95):95ra73.
26. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004;101(12):2788-2801.
27. Kantarjian HM, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia in second or subsequent complete remission. Leuk Lymphoma 2010;51(3):475-480.
28. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res 2007;13(2 Pt 1):559-565.
29. Kochenderfer JN, Dudley ME, Kassim SH, 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):540-549.
30. Larson SM, Campbell NP, Huo D, et al. High dose cytarabine and mitoxantrone: an effective induction regimen for high-risk acute myeloid leukemia (AML). Leuk Lymphoma 2012;53(3):445-450.
31. 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.
32. Lee DW, Gardner R, Porter DL, et al. *Erratum for* Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2015a;126(8):1048.
33. 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 2015b;385(9967):517-528.
34. 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):1507-1517.
35. Maus MV, Grupp SA, Porter DL, et al. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood 2014;123(17):2625-2635.
36. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. v1. 2014.
37. National Institutes of Health. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. 2013.
38. O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. Cancer 2008;113(11):3186-3191.
39. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-655.
40. Park JH, Riviere I, Wang X, et al. CD19 Targeted 1928z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B Cell ALL. 56th Annual Meeting of the American Society of Hematology. 2014; San Francisco, CA.
41. Pathak P, Hess R and Weiss MA. Liposomal vincristine for relapsed or refractory Ph-negative acute lymphoblastic leukemia: a review of literature. Ther Adv Hematol 2014;5(1):18-24.
42. Pinthus JH, Waks T, Malina V, et al. Adoptive immunotherapy of prostate cancer bone lesions using redirected effector lymphocytes. J Clin Invest 2004;114(12):1774-1781.
43. 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):1325-1331.
44. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med 2011;365(8):725-733.
45. Riviere I, Brose K and Mulligan RC. Effects of retroviral vector design on expression of human adenosine deaminase in murine bone marrow transplant recipients engrafted with genetically modified cells. Proc Natl Acad Sci U S A 1995;92(15):6733-6737.
46. Rodriguez V, Hart JS, Freireich EJ, et al. POMP combination chemotherapy of adult acute leukemia. Cancer 1973;32(1):69-75.
47. Sadelain M, Brentjens R and Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov 2013;3(4):388-398.
48. Schulert GS and Grom AA. Macrophage activation syndrome and cytokine-directed therapies. Best Pract Res Clin Rheumatol 2014a;28(2):277-292.
49. Schulert GS and Grom AA. Pathogenesis of Macrophage Activation Syndrome and Potential for Cytokine-Directed Therapies. Annu Rev Med 2014b.
50. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9-29.
51. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. Ann Hematol 2005;84(12):792-795.
52. Stachel D, Futterer A, Haas RJ, et al. Enhanced lymphocyte proliferation responses in pediatric patients early after myelosuppressive chemotherapy. Pediatr Blood Cancer 2004;43(6):644-650.

53. Stamenkovic I and 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):1205-1210.
54. Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia 2007;21(9):1907-1914.
55. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood 2013;121(26):5154-5157.
56. Thall PF and Simon R. Practical Bayesian guidelines for phase IIB clinical trials. Biometrics 1994;50(2):337-349.
57. Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. Cancer 1999;86(7):1216-1230.
58. Turk MJ, Guevara-Patino JA, Rizzuto GA, et al. Concomitant tumor immunity to a poorly immunogenic melanoma is prevented by regulatory T cells. J Exp Med 2004;200(6):771-782.
59. Turtle CJ, Berger C, Sommermeyer D, et al. Immunotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells of defined subset composition. Annual Meeting of the American Society of Clinical Oncology (2015), Chicago, IL.
60. 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.
61. Turtle CJ, Sommermeyer D, Berger C, et al. Therapy of B Cell Malignancies with CD19-Specific Chimeric Antigen Receptor-Modified T Cells of Defined Subset Composition. 56th Annual Meeting of the American Society of Hematology. 2014; San Francisco, CA.
62. Weiss MA. Treatment of adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL). Leukemia 1997;11 Suppl 4:S28-30.
63. Welborn JL. Impact of reinduction regimens for relapsed and refractory acute lymphoblastic leukemia in adults. Am J Hematol 1994;45(4):341-344.
64. Yao B, Zhu L, Jiang Q, et al. Safety monitoring in clinical trials. Pharmaceutics 2013;5(1):94-106.

Appendix A Schedule of Events (Part A)

Schedule of Events (Part A)	Protocol Section	Screening	Leukapheresis	Cytoreductive Chemotherapy[a]
Obtain informed consent		X		
Inclusion/exclusion criteria	5.1	X		
Concomitant medications[b]	8.3.3	X	X	X
Medical history, including confirmation of diagnosis, leukemia-specific history, stem cell transplant history (if applicable), and prior chemotherapy treatment		X		
Physical examination, including neurologic examination	8.3.2; 8.3.4	X		As clinically indicated
Vital signs including room air SaO_2	8.3.5.2	X	X	As clinically indicated
Height	8.3.5.3	X		
Weight	8.3.5.3	X	X	
ECOG performance status	8.3.5.4	X		
Echocardiogram/MUGA scan[c]	8.3.5.5	X		
12-Lead ECG	8.3.5.6	X[j]		
Chest x-ray	8.3.5.7	X		
Head CT or MRI[d]		As clinically indicated		
Neuropsychological assessment	8.3.4	X		
Local Laboratory Evaluations				
Serum chemistry	Appendix D	X[j]		As clinically indicated
Serum inflammation markers	Appendix D	X		
Hematology	Appendix D	X[j]		As clinically indicated
Serum pregnancy test[e]		X		
Viral serologies	Appendix D	X[j]		
Coagulation	Appendix D	X		As clinically indicated
Urinalysis	Appendix D	X		As clinically indicated
Serum immunoglobulins	Appendix D	X[j]		
Donor chimerism[f]	Appendix D	X[j]		
CSF assessment[g]	8.3.4	X[j]		

Schedule of Events (Part A)	Protocol Section	Screening	Leukapheresis	Cytoreductive Chemotherapy[a]
Bone marrow examination (aspirate and biopsy)		X		
Cytogenetics: Karyotyping and FISH (if data from current relapse not available)[h]		X		
HLA testing (if historical data are not available)[h]	Appendix D	X[j]		
BCR-ABL qPCR (peripheral blood or bone marrow)[i]		X[j]		
Intervention				
Leukapheresis	8.2.1.2		X	
Cytoreductive chemotherapy	6.2			X
Other supportive therapies while on study	6.4			As clinically indicated
Safety				
Serious adverse events	9.1	X	X	X
Biomarkers and PK	See Appendix C for details			

[a] Chemotherapy, if administered, should be initiated as soon as possible in order for marrow status to be determined at the time of JCAR015 availability

[b] Only concomitant medications used to treat SAEs will be recorded (see Section 8.3.3)

[c] Can be performed within 1 month prior to enrollment

[d] Head CT or MRI should be performed if clinical signs of CNS leukemia exist

[e] Within 7 days prior to the first dose of cytoreductive chemotherapy

[f] For subjects with history of allogeneic HSCT

[g] Prophylactic intrathecal chemotherapy may be given at the Investigator's discretion

[h] Historical data (no time limit) may be used. If historical data are not available, testing should be repeated.

[i] Required only for subjects with a history of Philadelphia chromosome-positive disease.

[j] Evaluations performed within 7 days prior to informed consent may be used to assess eligibility

Appendix B Schedule of Events (Part B)

Schedule of Events (Part B)	Protocol Section	Part B Screening	Lymphodepleting chemotherapy	JCAR015 Dose #1[a]	Post Dose #1							Lymphodepleting chemotherapy[b]	JCAR015 Dose #2[a]	Post Dose #2							Post-Infusion Monitoring: Post-Dose #2 (subjects that receive both infusions) or Post-Dose #1 (subjects that receive only one infusion)						Unscheduled Outpatient Visits	End of Study (EOS)	Upon Relapse
Scheduled Study Day		-18 to -2	-2	1	2	4	7	11	14	21[c]	28[c]	-5 to -2	1	2	4	7	11	14	21	28	60	90	120	150	180	270		360	
Scheduled Study Month																					2	3	4	5	6	9		12	
Visit Window (days)		NA	-3[d]			±1	±1	±1	±1	±2	±2	-3[d]			±1	±1	±1	±1	±2	±2	±14	±14	±14	±14	±14	±14		±14	
Inclusion/exclusion criteria	5.2	X																											
Concomitant medications	8.3.3	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	X	X	X
Physical examination[h]	8.3.2	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	X
Vital signs, including room air SaO_2[i]	8.3.5.2	X	X	X[f]	X	X	X	X	X	X	X	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X
Weight	8.3.5.3	X		X									X																
ECOG performance status	8.3.5.4	X		X			X		X	X	X		X			X		X	X	X	X	X	X	X	X	X		X[g]	X
MMSE	8.3.4	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X			X	X		X[g]	X
ECHO/MUGA scan	8.3.5.5	X[e]																											
12-Lead ECG	8.3.5.6	X[e]																											
Head CT or MRI		X[e]																			As clinically indicated								
Chest x-ray	8.3.5.7	X[e]																											
Neuropsychological assessment	8.3.4																				X[i]				X[i]			X[g,i,j]	X[j]

Schedule of Events (Part B)	Protocol Section	Part B Screening	Lymphodepleting chemotherapy	JCAR015 Dose #1[a]	Post Dose #1							Lymphodepleting chemotherapy[b]	JCAR015 Dose #2[a]	Post Dose #2						Post-Infusion Monitoring: Post-Dose #2 (subjects that receive both infusions) or Post-Dose #1 (subjects that receive only one infusion)						Unscheduled Outpatient Visits	End of Study (EOS)	Upon Relapse
Scheduled Study Day		-18 to -2	-2	1	2	4	7	11	14	21[c]	28[c]	-5 to -2	1	2	4	7	11	14	21	28	60	90	120	150	180	270		360	
Scheduled Study Month																					2	3	4	5	6	9		12	
Visit Window (days)		NA	-3[d]			±1	±1	±1	±1	±2	±2	-3[d]			±1	±1	±1	±1	±2	±2	±14	±14	±14	±14	±14	±14		±14	
Local Laboratory Evaluations																													
Serum chemistry	App D	X		X[n]	X	X	X	X	X	X	X		X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[g]	X
Hematology	App D	X		X[n]	X	X	X	X	X	X	X		X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[g]	X
Serum inflammation markers	App D			X[n]	X	X	X	X	X	X	X		X[n]	X	X	X	X	X	X	X		X							
Serum/urine pregnancy test		X																											
Coagulation	App D	X		X[n]			X		X	X	X		X[n]			X		X	X	X							X[e]		
Serum immunoglobulins (IgG, IgM, IgA)	App D	X							X		X							X		X		X			X		X[e]	X[g]	X
CSF clinical assessment	8.3.4	X[e]	As clinically indicated								X	As clinically indicated								X		X[e]			X[e]		X[e]	X[e,g]	X
Bone marrow examination (aspirate and biopsy) for morphologic assessment		X							X		X									X		X			X		X[e]	X[g]	X
BCR-ABL qPCR (peripheral blood or bone marrow)[m]									X		X									X		X			X		X	X[g]	X
Karyotyping and FISH																													X
Biomarker Assessments (see Appendix C for details)																													
Skin biopsy[k]		X																											

Schedule of Events (Part B)	Protocol Section	Part B Screening	Lymphodepleting chemotherapy	JCAR015 Dose #1[a]	Post Dose #1						Lymphodepleting chemotherapy[b]	JCAR015 Dose #2[a]	Post Dose #2							Post-Infusion Monitoring: Post-Dose #2 (subjects that receive both infusions) or Post-Dose #1 (subjects that receive only one infusion)						Unscheduled Outpatient Visits	End of Study (EOS)	Upon Relapse
Scheduled Study Day		-18 to -2	-2	1	2	4	7	11	14	21[c]	28[c]	-5 to -2	1	2	4	7	11	14	21	28	60	90	120	150	180	270		360	
Scheduled Study Month																					2	3	4	5	6	9		12	
Visit Window (days)		NA	-3[d]			±1	±1	±1	±1	±2	±2	-3[d]			±1	±1	±1	±1	±2	±2	±14	±14	±14	±14	±14	±14		±14	
Blood samples for biomarker analysis	App C (Table C-1)	X		X[n]	X	X	X		X	X	X		X	X	X	X		X	X	X	X	X			X			X[g]	X
Bone marrow specimens (aspirate and biopsy) for biomarker analysis	App C (Table C-2)	X							X		X									X		X			X			X[g]	X
CSF biomarker assessment	App C (Table C-3)										X									X		X[e]			X[e]			X[e,g]	X
QOL																													
FACT-Leu questionnaire		X									X									X		X			X	X		X[g]	X
Safety																													
Adverse events	9.1	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	X	X	X
RCR monitoring	7.9	X																				X			X			X[g]	X
Intervention																													
Lymphodepleting chemo	8.2.2.2		X									X[b]																	
JCAR015 infusion	6.3.12			X									X																
Other supportive therapies	6.4	ACI	As clinically indicated									As clinically indicated																	

ACI, as clinically indicated; App, appendix; MMSE, Mini Mental State Examination; RCR, replication-competent retrovirus

[a] Subjects experiencing toxicities from their preceding lymphodepleting chemotherapy may have their JCAR015 infusion schedule delayed up to 7 days (see Section 8.2.2.3 [Dose #1] or Section 8.2.2.6 [Dose #2]).

[b] For subjects with WBC count ≥ 1000/µL (at the discretion of the Investigator)

[c] For subjects who have not received Dose #2 by the indicated visit (i.e., Day 21 and/or Day 28 post-Dose #1)

[d] Lymphodepleting chemotherapy may occur between Day -5 and Day -2 (i.e., 2 to 5 days prior to JCAR015 administration)

[e] If clinically indicated

[f] Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured within approximately 15 minutes prior to, during, and within 15 minutes after the infusion; every 15 minutes thereafter for the first hour; and hourly for the next 3 hours. If the subject's vital signs are not stable 4 hours following JCAR015 infusion, vital signs should be monitored as clinically indicated until stable.

[g] Not required for subjects that withdraw from the study before receiving JCAR015

[h] Physical exam will include neurologic exam and assessment of CNS symptoms

[i] Window for neuropsychological assessment is ±28 days

[j] Only for subjects that withdraw prior to the Month 6 neuropsychological assessment

[k] Skin biopsy will be obtained in all subjects who consent to genetic testing. Skin biopsy will be obtained after cytoreductive chemotherapy to minimize contamination with blasts.

[l] Subjects who require hospitalization should have vital signs assessed daily. Minimum and maximum values within a 24-hour period should be recorded on the appropriate CRF.

[m] Required only for subjects with a history of Philadelphia chromosome-positive disease

[n] Prior to JCAR015 infusion

Appendix C Biomarker Sampling Schedule

Table C-1: Peripheral Blood Samples (Part B only)

Timepoint	CD19/CD22 quantification		Serum cytokines	ATA	Immuno-genicity (CTL)	Cellular PK		Immuno-phenotyping	Genomic analysis
						qPCR (persistence)	Flow (persistence)		
Part B Screening			X	X	X			X	X
Dose #1 Day 1 prior to infusion						X	X		
Post-Dose #1									
Day 2			X						X
Day 4 ± 1 day			X			X	X	X	
Day 7 ± 1 day			X			X	X	X	X
Day 14 ± 1 day			X		X	X	X	X	X
Before Dose #2[a,b]			X	X	X	X	X		
Post-Dose #2									
Day 2			X						X
Day 4 ± 1 day			X			X	X	X	
Day 7 ± 1 day			X			X	X	X	
Day 14 ± 1 day			X	X	X	X	X	X	X
Post-Final Dose (Post-Dose #1 for subjects who receive only 1 infusion, Post-Dose #2 for subjects who receive 2 infusions)									
Day 21 ± 2 days			X			X	X	X	
Day 28 ± 2 days			X	X	X	X	X	X	
Month 2 (± 14 days)						X	X		
Month 3 (± 14 days)				X	X	X	X		X
Month 6 (± 14 days)				X	X	X	X		X
EOS/Month 12 (± 14 days)				X	X	X	X		
Upon relapse	X							X	X

[a] Subjects who do not receive the second JCAR015 infusion should continue to have biomarker assessments scheduled through 12 months after the first infusion according to the timepoints indicated (i.e., starting at the Post-Final Dose Day 21 visit through the Post-Final Dose Month 12 visit)

[b] To be collected at the Dose #2 Day 1 visit prior to the second JCAR015 infusion.

Table C-2: Bone Marrow Aspirate/Biopsy and Skin Biopsy Samples

Timepoint	Bone Marrow Aspirate				Bone Marrow Biopsy	Skin biopsy[b]
	CD19/CD22 quantification	MRD	qPCR (persistence)	Genomic analysis	Immunohisto-chemistry[a]	
Part A Screening	X	X		X	X	
Part B Screening		X	X			X
Post-Dose #1						
Day 14 (±1 day)		X	X	X	X	
Day 28 (± 2 days)[c]		X	X	X	X	
Post-Final Dose (Post-Dose #1 for subjects who receive only 1 infusion, Post-Dose #2 for subjects who receive 2 infusions)						
Day 28 (± 2 days)[d]		X	X	X	X	
Month 3 (± 14 days)		X	X	X	X	
Month 6 (± 14 days)		X	X	X	X	
EOS/Month 12 (± 14 days)		X	X		X	
Upon relapse	X			X	X	

[a] Immunohistochemistry will be performed on bone marrow biopsy specimens, not aspirate

[b] Only for subjects that consent to genetic testing

[c] Only for subjects that have not received a second dose of JCAR015 by Post-Dose #1 Day 28

[d] Only for subjects that receive a second dose of JCAR015

Table C-3: Cerebrospinal Fluid Samples

Timepoint	qPCR (persistence)
Part A Screening	X
Day 28 Post-Final Dose (± 2 days)[a]	X
Month 3 (± 14 days)[b]	X
Month 6 (± 14 days)[b]	X
End of study/Month 12 (± 14 days)[a,b]	X
Upon relapse	X

[a] Post-Dose #1 for subjects who receive only one infusion, Post-Dose #2 for subjects who receive two infusions

[b] Only if clinically indicated

Appendix D Local Clinical Laboratory Evaluations

Laboratory Panel	Analytes
Serum chemistry	Glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, CO_2, LDH, uric acid, triglycerides
Hematology	CBC with differential
Coagulation	PT, aPTT, INR, fibrinogen, and D-dimer
Urinalysis	Appearance, pH, specific gravity, protein Glucose, ketones, RBCs, WBCs Casts, crystals, or other components
Viral serology	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb) Hepatitis C (Hep C Ab)
HLA typing	HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1
Serum markers of inflammation	CRP, ferritin
Donor chimerism	% stem cell donor
Disease characterization	ALL cytogenetics, FISH, BCR-ABL qPCR (for Ph+ disease), tumor immunophenotyping (flow cytometry)
Cerebrospinal fluid	Erythrocytes (RBCs), leukocytes (WBCs) with differential, glucose, protein
Serum immunoglobulins	IgG, IgM, IgA

Appendix E Cockcroft-Gault Equation for Calculating Estimated Creatinine Clearance

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Males	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Females	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
µM/dL	Males	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (µM/dL)}}$
	Females	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (µM/dL)}}$

Appendix F FACT-Leu version 4 Questionnaire

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
BS3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

Appendix G Response Criteria for Acute Lymphoblastic Leukemia

Response Category	Criteria
CR	All of the following criteria must be met: • Bone marrow – Trilineage hematopoiesis and < 5% blasts[a] • Peripheral blood – Neutrophils > 1,000/µL – Platelets > 100,000/µL – Circulating blasts < 1% • Extramedullary disease – No clinical evidence of extramedullary disease by physical examination; no symptoms suggestive of CNS involvement – If additional assessments are required (e.g., CSF assessment by lumbar puncture or Ommaya reservoir tap, CNS imaging, biopsy) and are performed, results must show no evidence of disease • Transfusion dependency – No platelet and/or neutrophil transfusions ≤ 7 days before the date of peripheral blood sampling for disease assessment • No clinical evidence of recurrence for 4 weeks
CRi	All of the criteria indicated above for CR are met, except that the following exist: • Peripheral blood – Neutrophils ≤ 1,000/µL, or – Platelets ≤ 100,000/µL, or – Platelet transfusions ≤ 7 days before the date of peripheral blood sampling for disease assessment
Relapsed disease	Only valid in patients who achieved a CR or CRi and in whom there exists: • Reappearance of blasts in the peripheral blood (≥ 1%), or • Reappearance of blasts in the bone marrow (≥ 5%)[a], or • Appearance/reappearance of any extramedullary disease after CR or CRi
No response	Failure to attain the criteria specified above for any response categories or relapse
Unknown	Assigned only in cases where the baseline assessment or the response assessment is not performed, is incomplete, is indeterminate, or is not performed within the protocol-specified time frame (i.e., from informed consent through 12 months after the final JCAR015 infusion)

a Blast percentage can be determined from a bone marrow aspirate and also estimated from a bone marrow biopsy. In the event that both aspirate and biopsy results are available, the blast percentage used for response assessment should be based on the bone marrow aspirate. In the event that only one sample is available (aspirate or biopsy, but not both) with non-missing values, the result of the non-missing assessment will be used to assess response.

Appendix H Mini Mental State Examination (2nd Edition)

MMSE-2

Standard Version

Blue Form

Date of examination ____/____/____ Examiner _____

Name _____ Age _____ Sex _____

Years of school completed _____ Purpose of exam _____

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Unless otherwise specified, circle 0 if the response is incorrect or 1 if the response is correct. Begin by introducing the test:

Now I'd like to ask you some questions about your memory.

	RESPONSE	SCORE (circle one)
REGISTRATION		
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... MILK [*pause*], **SENSIBLE** [*pause*], **BEFORE** [*pause*]. **Now repeat those words back to me.** [*Repeat up to 3 times, but score only the first trial.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.		
ORIENTATION TO TIME		
What day is today? What is the...		
year?		0 1
season?		0 1
month of the year?		0 1
day of the week?		0 1
date?		0 1
ORIENTATION TO PLACE*		
Where are we now? What is the...		
state (or province)?		0 1
county (or city/town)?		0 1
city/town (or part of city/neighborhood)?		0 1
building (name or type)?		0 1
floor of the building (room number or address)?		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

RECALL		
What were those three words I asked you to remember? [*Do not offer any hints.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1

If administering the MMSE-2:SV, copy the MMSE-2:BV total raw score to the space provided at the top of page 2 and continue with administration.

MMSE-2:BV total raw score ____ (30 max. points)

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MMSE-2:BV total raw score ____ (16 max. points)

ATTENTION AND CALCULATION [*Serial 7s*]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	0	1
If needed, say: **Keep going.**	[86]	0	1
If needed, say: **Keep going.**	[79]	0	1
If needed, say: **Keep going.**	[72]	0	1
If needed, say: **Keep going.**	[65]	0	1

Score 1 point for each correct answer. An answer is considered correct if it is 7 less than the previous answer, even if the previous answer was incorrect.

NAMING

What is this? [*Point to eye.*]	0	1
What is this? [*Point to ear.*]	0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? IT IS A LOVELY, SUNNY DAY BUT TOO WARM. Now you say that. [*Wait for examinee response and record response verbatim. Repeat up to one time.*]

IT IS A LOVELY, SUNNY DAY BUT TOO WARM.	0	1

Detach the last page of this form. Tear the detached page in half along the horizontal perforation line. Use the upper half of the detached page, which has three shapes on it, as a stimulus form for the Comprehension task. Use the bottom half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") task. Use the upper back half of the detached page as a stimulus and response form for the Drawing (intersecting pentagons) task and the bottom half of the page (blank) as a response form for the Writing task.

COMPREHENSION

Listen carefully because I am going to ask you to do something. [*Show examinee the geometric figures stimulus page.*] **Look at these pictures and point to the circle, then point to the square, and then point to the triangle.**

Correct response	Observed response		
○		0	1
□		0	1
△		0	1

READING

[*Show examinee the word stimulus page.*] **Please do what this says to do.**

CLOSE YOUR EYES	0	1

WRITING

[*Place the blank piece of paper in front of the examinee and provide a pen or pencil.*] **Please write a sentence.** [*If examinee does not respond, say:* **Write about where you live.**] 0 1

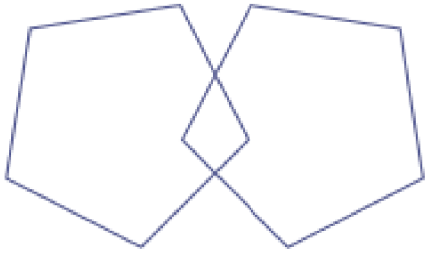
Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

MMSE-2:SV total raw score ____ (30 max. points)

CLOSE YOUR EYES



1 OVERALL SUMMARY OF CHANGES

1.1 Amendment 5

Amendment 5 of Protocol 015001 was initiated in response to a fatal event of cerebral edema in association with severe cytokine release syndrome (sCRS) in a subject (Subject) who received JCAR015 following lymphodepleting chemotherapy with cyclophosphamide in combination with fludarabine. As a result of this event, the following changes were made to the protocol:

- Guidelines for the management of cytokine release syndrome (CRS) and neurotoxicity were revised and the management algorithm for CRS was updated.

Prior to finalization of the amendment, two additional subjects who received JCAR015 following lymphodepleting chemotherapy with the fludarabine/cyclophosphamide lymphodepleting chemotherapy regimen died due to cerebral edema. A teleconference was held with the Food and Drug Administration (FDA) on 06 July 2016. As a result of this teleconference and discussion with the Data Safety Monitoring Board (DSMB), the following additional changes were incorporated into Amendment 5 of the protocol (submitted to the FDA on 08 July 2016):

- The lymphodepleting chemotherapy regimen consisting of fludarabine in combination with cyclophosphamide was removed. Single-agent cyclophosphamide will now be the only allowed regimen for lymphodepleting chemotherapy. The primary efficacy analysis set was updated accordingly to include morphologic subjects who receive JCAR015 following lymphodepleting chemotherapy with cyclophosphamide alone. The sample size was adjusted to ensure that a minimum of 50 subjects are included in the primary efficacy analysis set.
- A summary of safety findings from the eight subjects who were treated on the 015001 protocol with JCAR015 following lymphodepleting chemotherapy with fludarabine and cyclophosphamide was added (Section 1.5). The results from these subjects were compared with the 14 subjects treated in this study with JCAR015 following lymphodepletion with cyclophosphamide alone, as well as with subjects treated on MSKCC Protocol 09-114. These analyses supported removal of fludarabine from the lymphodepleting chemotherapy regimen.
- Upon resuming enrollment of subjects to the protocol, gating will be implemented for the first six subjects eligible for treatment, such that only one subject across all sites may be treated in any calendar week until six subjects have been treated with JCAR015 and cyclophosphamide and followed for at least 14 days after the first JCAR015 dose. For subjects below the age of 30, gating will continue until six subjects under the age of 30 have been treated.

The following additional changes were also made in Amendment 5:

- Analysis of minimal residual disease (MRD) by flow cytometry in peripheral blood samples was removed.
- Subjects will be asked at the time of informed consent to consent to autopsy in the event of their death.

- Administration of lymphodepleting chemotherapy prior to the second JCAR015 dose for subjects whose white blood cell count is ≥1000/µL was changed from being required to administered at the discretion of the Investigator.
- Clarification was made that RCR testing will be conducted at the relapse visit, if applicable.
- Language was added specifying that in situations where samples for biomarker analysis are insufficient, modifications in allocation of samples for biomarker analysis may be made.
- Clarification was made that AEs are assessed for relationship to lymphodepleting chemotherapy in addition to JCAR015.

1.2 Amendment 5.1

Upon notification from the FDA on 12 July 2016 that the trial was allowed to proceed, the following administrative changes were made as Amendment 5.1 prior to submission to study sites:

- Clarification was made that leukapheresis may be performed prior to completion of screening procedures.
- Minor wording changes were made to the description of the JCAR015 investigational product to align with changes made in version 4 of the JCAR015 Investigator's brochure.
- Clarification was made that prior to each JCAR015 infusion, subjects should be pre-medicated with either acetaminophen or diphenhydramine or both at the discretion of the Investigator.
- Timeframe for conducting MUGA scan or echocardiogram was changed from within 8 weeks of screening to within 1 month of enrollment for consistency with the eligibility criteria.
- Clarification was made that subjects who relapse before the end-of-study visit may either continue on the study or withdraw from the study and enroll on the long-term follow-up protocol.

1 OVERALL SUMMARY OF CHANGES

Amendment 4 of Protocol 015001 was prepared primarily to update the analysis set for the primary efficacy analysis to include only subjects with morphologic disease who are intended to receive lymphodepleting chemotherapy with fludarabine plus cyclophosphamide. This analysis set was renamed the "Primary Efficacy Analysis Set." To ensure that a sufficient number of subjects are enrolled for this analysis, the overall number of subjects planned for enrollment was increased from 90 to 110. These changes were made in response to emerging data indicating that use of fludarabine/cyclophosphamide conditioning may provide for improved responses to JCAR015, and to ensure a homogeneous population for evaluation the primary objective.

The following additional changes were also made to the protocol:

- Language specifying that only a single cycle of cytoreductive chemotherapy will be administered in Part A was removed.
- Clarification was made that delays in JCAR015 treatment are permitted to allow for recovery from intercurrent illness, in addition to toxicity, following cytoreductive chemotherapy or the first JCAR015 infusion.
- Clarification was made that a bone marrow examination must be performed within 10 days prior to initation of lymphodepleting chemotherapy.
- Clarification was made that subjects who are withdrawn from the study prior to receiving JCAR015 due to prolonged illness and subsequently re-enroll are not required to undergo a second leukapheresis if they have an available JCAR015 cell product that met release criteria.
- Text was added specifying that a water bath or other thawing method is not allowed for thawing JCAR015 cell product.
- Windows for study visits conducted from 2 months after the final JCAR015 infusion through the end-of-study (EOS) visit were increased from ± 7 days to ± 14 days.
- Clarification was made regarding the weight measurement to be used for manufacturing and dosing of JCAR015 cell product.
- Contact information for the new Juno manufacturing facility was provided.
- Other minor administrative changes were made for clarity and consistency across the protocol sections.

1 OVERALL SUMMARY OF CHANGES

Amendment 3 of Protocol 015001 was prepared to address investigator feedback regarding lymphodepleting chemotherapy and prior treatment with blinatumomab. Briefly, the following substantive changes were made to the protocol:

- A dosing schedule for administration of lymphodepleting chemotherapy with cyclophosphamide and fludarabine was added for subjects enrolled after the interim analysis cohort is accrued.
- Language for inclusion criteria was modified to allow failure following prior treatment with blinatumomab to be considered as a standard regimen for the purpose of defining refractory ALL.
- Collection of blood samples for baseline analysis of cellular pharmacokinetics by flow cytometry and qPCR were moved from Part B screening to preinfusion on the day of the first JCAR015 infusion.

In addition, other minor administrative changes and typographical corrections were made.

1 OVERALL SUMMARY OF CHANGES

Amendment 2 of Protocol 015001 was prepared to address regulatory and investigator feedback, provide a second lymphodepleting chemotherapy regimen based on emerging Phase 1 clinical trial data, and enhance overall clarity. Briefly, the following substantive changes were made to the protocol:

- The inclusion criteria were modified for subjects who have had a prior allogeneic hematopoetic stem cell transplant (HSCT).
- The inclusion criteria were modified to require that evidence of CD19 expression be confirmed from a leukemia sample obtained from the current relapse.
- The combination of cyclophosphamide and fludarabine was added as the regimen for lymphodepleting chemotherapy for subjects enrolled after the interim analysis cohort is accrued.
- Corrections and clarifications were made to the assessments listed in the study visits section of the protocol (Section 8.2) and in the schedule of assessments tables (Appendix A and Appendix B) for consistency and clarity.

In addition, other minor clarifications, administrative changes, and typographical corrections were made to the text.

1 OVERALL SUMMARY OF CHANGES

Amendment 1 of Protocol 015001 was prepared to address regulatory and investigator feedback, to augment adverse event monitoring and safety stopping/pausing rules, and to enhance overall clarity. Briefly, the following changes were made to the protocol:

- Included safety monitoring boundaries based on Grade 3 and 4 treatment-related adverse events of special interest, which, if crossed, requires a pause in enrollment pending review by the Data Safety Monitoring Board
- Added neuropsychological testing at baseline and at 2 and 6 months following final JCAR015 infusion; added guidelines for seizure prophylaxis with levetiracetam
- Added detailed rationale for JCAR015 dosing regimen, including data from preclinical and clinical studies regarding relationships between CAR T cell dose and response; CAR T cell dose, disease burden, and toxicity; and CAR T cell persistence and duration of response.
- Added guidance and rationale for specifying a dose range for cyclophosphamide rather than a single dose
- Added a range to the recommended tocilizumab (4 to 8 mg) for treatment of cytokine release syndrome (CRS)
- Clarified that specified JCAR015 doses are *target* doses and may not reflect the final cell number administered
- Added Mini Mental Status Examination (MMSE) to neurologic examination at specified timepoints
- Added Ommaya tap as a possible procedure for obtaining cerebrospinal fluid
- Added language to specify that subjects clinically unfit to receive JCAR015 at the end of Part A should be withdrawn from the study
- Added language to specify that subjects who undergo hematopoietic stem cell transplant should be withdrawn from the study and enrolled on the long-term follow-up protocol
- Specified that a delay of up to 8 weeks is permissible for subjects needing extra time to arrange travel to the study site
- Changed thaw time for frozen JCAR015 product bags from a range of 20 to 30 minutes to 30 minutes
- Added text specifying the number of JCAR015 product bags used for each JCAR015 administration
- Clarified language regarding recording of concomitant medications
- Clarified language to reflect the occurrence of neurologic symptoms in the absence of severe cytokine release syndrome (sCRS)
- Specified that the assessment of comparability between subjects receiving 1928z cell product in the MSKCC Phase 1 Study 09-114 and subjects receiving JCAR015 cell product in the current study (015001) is descriptive in nature and no formal statistical comparisons will be done

- Added the FACT-Leu questionnaire at Post-Dose #1 Day 28 and Post-Dose #2 Day 28
- Moved timing of skin biopsy from Part A screening to Part B screening
- Removed “p210” from all instances of “p210 BCR ABL”
- Clarified that Part A exclusion criteria for chronic myelogenous leukemia (CML) lymphoid blast crisis is p210 BCR-ABL-positive
- Modified some instances of the term “PK” to “cellular PK”

In addition, other minor clarifications, administrative changes, and typographical corrections were made to the text.